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Coffey

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(54) **REOVIRUSES HAVING MODIFIED SEQUENCES**

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(51) **Int. Cl.**
A61K 39/15 (2006.01)

(52) **U.S. Cl.**
USPC **424/215.1; 424/93.3**

(58) **Field of Classification Search**
None
See application file for complete search history.

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(57) **ABSTRACT**

The invention provides for modified reovirus nucleic acid sequences and modified reovirus polypeptide sequences as well as reoviruses containing such modified nucleic acid or polypeptide sequences. The invention also provides for pharmaceutical compositions that include reoviruses having a modified sequence as well as methods of making and using such reoviruses.

20 Claims, 12 Drawing Sheets

Figure 1-1

S1:

GCTATTGGTCGGATGGATCCTCGCCTACGTGAAGAAGTAGTACGGCTGATAATCGCATTAACGAGTGATAA
TGGAGCATCACTGTCAAAAGGGCTTGAATCAAGGGTCTCGGCGCTCGAGAAGACGTCTCAAATACACTCTG
ATACTATCCTCCGGATCACCCAGGGACTCGATGATGCAAACAAACGAATCATCGCTCTTGAGCAAAGTCGG
GATGACTTGGTTGCATCAGTCAGTGATGCTCAACTTGCAATCTCCAGATTGGAAAGCTCTATCGGAGCCCT
CCAAACAGTTGTCAATGGACTTGATTTCGAGTGTTACCCAGTTGGGTGCTCGAGTGGGACAACCTTGAGACAG
GACTTGCAGAGCTACGCGTTGATCACGACAATCTCGTTGCGAGAGTGGATACTGCAGAACGTAACATTGGA
TCATTGACCACTGAGCTATCAACTCTGACGTTACGAGTAACATCCATACAAGCGGATTTTGAATCTAGGAT
ATCCACGTTAGAGCGCACGGCGGTCACTAGCGCGGGAGCTCCCCCTCTCAATCCGTAATAACCGTATGACCA
TGGGATTAAATGATGGACTCACGTTGTCAGGGAATAATCTCGCCATCCGATTGCCAGGAAATACGGGTCTG
AATATTCAAAATGGTGGACTTCAGTTTCGATTTAATACTGATCAATTCAGATAGTTAATAATAACTTGAC
TCTCAAGACGACTGTGTTTGATTCTATCAACTCAAGGATAGGCGCAACTGAGCAAAGTTACGTGGCGTCGG
CAGTGACTCCCTTGAGATTAAACAGTAGCACGAAGGTGCTGGATATGCTAATAGACAGTTCAACACTTGAA
ATTAATTCTAGTGGACAGCTAACTGTTAGATCGACATCCCCGAATTTGAGGTATCCGATAGCTGATGTTAG
CGGCGGTATCGGAATGAGTCCAAATTATAGGTTTAGGCAGAGCATGTGGATAGGAATTGTCTCCTATTCTG
GTAGTGGGCTGAATTGGAGGGTACAGGTGAACTCCGACATTTTTATTGTAGATGATTACATACATATATGT
CTTCCAGCTTTTTGACGGTTTTCTCTATAGCTGACGGTGGAGATCTATCGTTGAACTTTGTTACCGGATTGTT
ACCACCGTTACTTACAGGAGACACTGAGCCCGCTTTTCATAATGACGTGGTCACATATGGAGCACAGACTG
TAGCTATAGGGTTGTCGTCGGGTGGTGCGCCTCAGTATAIGAGTAAGAATCTGTGGGTGGAGCAGTGGCAG
GATGGAGTACTTCGGTTACGTGTTGAGGGGGGTGGCTCAATTACGCACTCAAACAGTAAGTGGCCTGCCAT
GACCGTTTCGTACCCGCGTAGTTTTCACGTGAGGATCAGACCACCCCGCGGCACTGGGGCATTTTCATC
(SEQ ID NO:1)

S2:

GCTATTCGCTGGTCAGTTATGGCTCGCGCTGCGTTCCTATTCAAGACTGTTGGGTTTGGTGGTCTGCAAAA
TGTGCCAATTAACGACGAACATCTTACATCTACTCCGAGCTGGTAATTCACCATGGCAGTTAACACAGT
TTTTAGACTGGATAAGCCTTGGGAGGGGTTTAGCTACATCGGCTCTCGTTCCGACGGCTGGGTCAAGATAC
TATCAAATGAGTTGCCTTCTAAGTGGCACTCTCCAGATTCCGTTCCGTCCTAACCACCGATGGGGAGACAT
TAGGTTCTTACGCTTAGTGTGGTCAGCTCCTACTCTCGATGGATTAGTCGTAGCTCCACCACAAGTTTTGG
CTCAGCCCCGCTTTGCAAGCACAGGCAGATCGAGTGACGACTGCGATGATTATCCATTTCTAGCGCGTGAT
CCAAGATTCAAACATCGGGTGTATCAGCAATTGAGTGCTGTAACCTCTACTTAACTTGACAGGTTTTGGCCC
GATTTCTTACGTTTCGAGTGGATGAAGATATGTGGAGTGGAGATGTGAACCAGCTTCTCATGAACTATTTG
GGCACACGTTTGCAGAGATTGCATACACATTGTGTCAAGCCTCGGCTAATAGGCCTTGGGAATATGACGGT
ACATATGCTAGGATGACTCAGATTGTGTTATCCTTGTTCTGGCTATCGTATGTCGGTGTAAATTCATCAGCA
GAATACGTATCGGACATTCTATTTTCAGTGTAATCGGCGAGGTGACGCCGCTGAGGTGTGGATTCTTTCTT
GTTCTGTTGAACCATTCCGCACAAATTAGACCGGGTAATCGTAGCTTATTCTGTTATGCCAACTAGCCCAGAT
TGGAACATGGACGTCAATTTGATCCTGAGTTCAACGTTGACGGGGTGTGTTGTGTTTCGGGTTTCACAGCTGCC
ACTGATTGACAATAATTCAGTACCTGCAGTGTCGCGTAACATCCATGGCTGGACTGGTAGAGCTGGTAACC
AATTGCATGGGTTCAGGTGAGACGAATGGTGACTGAATTTTGTGACAGGTTGAGACGCGATGGTGTCTATG
ACCCAAGCTCAGCAGAATCAAGTTGAAGCGTTGGCAGATCAGACTCAACAGTTTAAGAGGGACAAGCTCGA
AACGTGGGCGAGAGAAGACGATCAATATAATCAGGCTCATCCCAACTCCACAATGTTCCGTACGAAACCAT
TTACGAATGCGCAATGGGGACGAGGTAATACGGGGGCGACTAGTGCCGCGATTGCAGCCCTTATCTGATCG
TCTTGGAGTGAGGGGGTCCCCCACACACCTCACGACTGACCACACATTCATC (SEQ ID NO:2)

S3:

GCTAAAGTCACGCCTGTCGTCGTCACCTATGGCTTCCTCACTCAGAGCTGCGATCTCCAAGATCAAGAGGGA
TGACGTCGGTCAGCAAGTTTGTCTTAATTATGTCATGCTGCGGTCTCTGTACACAACAAAGGTGGTACGAA
ATGTGGTTGAGTATCAAATTCGTACGGGCGGATTCTTTTCGTGCTTAGCTATGCTAAGGCCACTCCAGTAC
GCTAAGCGTGAGCGTTTGTCTGGTCAGAGGAATCTGGAACGTATATCGACTAGGGATATCCTTCAGACTCG
TGATTTACACTCACTATGTATGCCAACTCCTGATGCGCCAATGTCTAATCATCAAGCATCCACCATGAGAG
AGCTGATTTGCAGTTACTTCAAGGTGATCATGCGGATGGGTGAAATATATACCCATGGATGAGAGATAC

Figure 1-2

TCTCCGTCATCACTTGCCAGATTGTTTACCATGGGCATGGCTGGGCTGCACATTACCACTGAGCCATCTTA
TAAGCGTGTTCCGATTATGCACTTAGCTGCGGACTTGGACTGTATGACGCTGGCTCTACCTTACATGATTA
CGCTTGATGGTGATACTGTGGTTCCTGTGCTCCAACACTGTCAGCGGAACAGCTTCTGGACGACGGACTC
AAAGGATTAGCATGCATGGATATCTCCTATGGATGTGAGGTGGACGCGAATAGCCGGCCGGCTGGTGATCA
GAGTATGGACTCTTCACGCTGCATCAACGAGTTGTATTGCGAGGAGACAGCAGAAGCCATCTGTGTGCTTA
AGACATGCCTTGTGTTAAATTGCATGCAGTTTAACTTGAGATGGATGACCTAGCACATAACGCTGCTGAG
CTGGACAAGATACAGATGATGATACCCCTCAGTGAGCGTGTTTTTAGGATGGCCTCGTCCTTTGCGACTAT
TGATGCCCAGTGTTTTAGGTTTTGCGTGATGATGAAGGATAAAAAATCTGAAAATAGATATGCGTGAAACGA
CGAGACTGTGGACTCGTTCAGCATCAGATGATTCTGTGGCCACGTCATCTTTAAGTATTTCCCTGGACCGG
GGTCGATGGGTGGCGGCTGACGCCAGTGATGCTAGACTGCTGGTTTTTCCGATTGCGGTGTAATGGGTGAG
TGAGCTGATGTGGTCGCCAAGACATGTGCCGGTGTCTTGGTGGTGGGTGACGCCTAATCATC (SEQ ID
NO:3)

S4:

GCTATTTTTGCCTCTTCCCAGACGTTGTGCGCAATGGAGGTGTGCTTGCCCAACGGTCATCAGGTCGTGGAC
TTAATTAACAACGCTTTTGAAGGTGCTGTATCAATCTACAGCGCGCAAGAGGGATGGGACAAAACAATCTC
AGCACAGCCAGATATGATGGTATGTGGTGGCGCCGTCGTTTGCATGCATTGTCTAGGTGTTGTTGGATCTC
TACAACGCAAGCTGAAGCATTTGCCTCACCATAGATGTAATCAACAGATCCGTCATCAGGATTACGTCGAT
GTACAGTTCGCAGACCGTGTTACTGCTCACTGGAAGCGGGGTATGCTGTCTTTCGTTGCGCAGATGCACGA
GATGATGAATGACGTGTGCGCCAGATGACCTGGATCGTGTGCGTACTGAGGGAGGTTCACTAGTGGAGCTGA
ACCGGCTTCAGGTTGACCCAAATTCAATGTTTATGATCAATACTCAAGTTGGACAGATCCTTTGCAGGTG
GTGGACGACCTTGACACTAAGCTGGATCAGTACTGGACAGCCTTAAACCTGATGATCGACTCATCCGACTT
GATACCCAACCTTTATGATGAGAGACCCATCACACGCGTTCAATGGTGTGAACTGAAGGGAGATGCTCGTC
AAACCCAATTCTCCAGGACTTTTGATTGAGATCGAGTTTGGAATGGGGTGTGATGGTTTTATGATTACTCT
GAGCTGGATCATGATCCATCGAAGGGCCGTGCTTACAGAAAGGAATTGGTGACGCCAGCTCGAGATTTCCG
TCACTTTGGATTATCCCATTATTCTAGGGCGACTACCCCAATCCTTGGAAAGATGCCGGCCGTATTCTCAG
GAATGTTGACTGGGAACTGTAAAATGTATCCATTTCATTAAAGGAACGGCTAAGCTGAAGACAGTGCGCAAG
CTAGTGGAGGCAGTCAATCATGCTTGGGGTGTGCGAGAAGATTAGATATGCTCTTGGGCCAGGTGGCATGAC
GGGATGGTACAATAGGACTATGCAACAGGCCCCCATTTGTGCTAACTCCTGCTGCTCTCACAATGTTCCAG
ATACCATCAAGTTTGGGGATTTGAATTATCCAGTGATGATTGGCGATCCGATGATTCTTGGCTAAACACCC
CCATCTTCACAGCGCCGGGCTTGACCAACCTGGTGTGACGTGGGACAGGCTTCATTCATC (SEQ ID
NO:4)

Figure 2-1

M1 :

GCTATTTCGCGGTCATGGCTTACATCGCAGTTCCTGCGGTGGTGGATTACGTTTCGAGTGAGGCTATTGGAC
TGCTAGAATCGTTTGGAGTAGACGCTGGGGCTGACGCGAATGACGTTTCATATCAAGATCATGACTATGTG
TTGGATCAGTTACAGTACATGTTAGATGGATATGAGGCTGGTGACGTTATCGATGCACTCGTCCACAAGAA
TTGGTTACATCACTCTGTCTATTGCTTGTGTCACCCAAAAGTCAACTATTAGAGTATTGGAAAAGTAATC
CTTCAGCGATACCGGACAACGTTGATCGTCGGCTTCGTAAACGACTAATGCTAAAGAAAGATCTCAGGAAA
GATGATGAATACAATCAGCTAGCGCGTGCTTTCAGATATCGGATGTCTACGCACCTCTCATCTCATCCAC
GACGTCACCGATGACAATGATACAGAACTTGAATCGAGGCGAGATCGTGTACACCACGACGGACAGGGTAA
TAGGGGCTAGAATCTTGTTATATGCTCCTAGAAAGTACTATGCGTCAACTCTGTCAATTTACTATGACTAAG
TGCATCATTCCGTTTGGTAAAGAGGTGGGTGCTGTTTCTCACTCTCGATTTAATGTTGGCACATTTCCGTC
AATTGCTACCCCGAAAATGTTTTGTCATGAGTGGGGTTGATATTGAGTCCATCCCAAATGAATTTATCAAGT
TGTTTTTACCAGCGCGTCAAGAGTGTTCACGCTAACATACTAAATGACATATCTCCTCAGATCGTCTCTGAC
ATGATAAACAGAAAGCGTCTGCGCGTTCATACTCCATCAGATCGTCGAGCCGCGCAGTTGATGCATTTGCC
TTACCATGTTAAACGAGGAGCGTCTCACGTGACGTTTACAAGGTGGATGTTGTAGACATGTTGTTTCGAGG
TAGTGGATGTGGCCGATGGGTGCGCAACGTATCTAGGAACTAACTATGCATACCGTTCCTGTATGTATT
CTTGAAATGTTGGGTATTGAGATTGCGGACTATTGCATTCGTCAAGAGGATGGAATGCTCACAGATTGGTT
CCTACTTTTAAACCATGCTATCTGATGGCTTGACTGATAGAAGGACGCATTGTCAATACTTGATTAATCCGT
CAAGTGTGCCTCCTGATGTGATACTTAACATCTCAATTACTGGATTTATAAATAGACATACAATCGATGTC
ATGCCTGACATATATGACTTCGTTAAACCCATTGGCGCTGTGCTGCCTAAGGGATCATTTAAATCAACAAT
TATGAGAGTTCCTGATTCAATATCAATATTAGGAATCCAAATCATGCCGCGCGCGCATGTAGTTGACTCAG
ATGAGGTGGGCGAGCAAATGGAGCCTACGTTTGAGCAGGCGGTTATGGAGATATACAAAGGGATTGCTGGC
GTTGACTCGCTGGATGATCTCATCAAGTGGGTGTTGAACTCGGATCTCATTCCGCATGATGACAGGCTTGG
TCAATTATTTCAAGCGTTTTTGCCTCTCGCAAAGGACTTATTAGCTCCAATGGCCAGAAAGTTTTATGATA
ACTCAATGAGTGAGGGTAGATTGCTAACATTCTCTCATGCCGACAGTGAGTTGCTGAACGCAAATTATTTT
GGTCATTTATTGCGACTAAAAATACCATATATTACAGAGGTTAATCTGATGATTTCGCAAGAATCGTGAGGG
TGGAGAGCTATTTTCAGCTTGTGTTATCTTATCTATATAAAATGTATGCTACTAGCGCGCAGCCTAAATGGT
TTGGATCATTATTGCGATTGTTAATATGTCCCTGGTTACATATGGAGAAATTAATAGGAGAAGCAGACCCG
GCATCTACGTCGGCTGAAATTGGGTGGCATATCCCTCGTGAACAGCTGATGCAAGATGGATGGTGTGGATG
TGAAGACGGATTTCATTCCCTATGTTAGCATACGTGCGCCAAGACTGGTTATAGAGGAGTTGATGGAGAAGA
ACTGGGGCCAATATCATGCCCAAGTTATTGTCACTGATCAGCTTGTCTGATAGGCGAACC CGGAGGGTATCT
GCTAAGGCTGTGATCAAGGGTAACCACTTACCAGTTAAGTTAGTTTTCACGATTTGCATGTTTCACATTGAC
GGCGAAGTATGAGATGAGGCTTTCGTGCGGCCATAGCACTGGACGTGGAGCTGCATACAGTGCGAGACTAG
CTTTCCGATCTGACTTGGCGTGATCCGTGACATGCGTAGTGTGACACCTGCTCCTAGGTCAATGGGGGTAG
GGGGCGGGCTAAGACTACGTACGCGCTTCATC (SEQ ID NO:5)

M2 :

GGCTAATCTGCTGACCGTTACTCTGCAAAGATGGGGAACGCTTCCTCTATCGTTTCAGACGATCAACGTCAC
TGGAGATGGCAATGTATTTAAACCATCAGCTGAAACTTCATCTACCGCTGTACCATCGTTAAGCTTATCAC
CTGGAATGCTGAATCCCGGAGGGGTACCATGGATTGCTGTTGGAGATGAGACATCTGTGACTTCACCAGGC
GCATTACGTCGAATGACGTCAAAGGACATCCCGGACACGGCAATAATCAACACAGACAATTCATCAGGCGC
CGTGCCAAGCGAATCAGCCTTGGTGCCCTACATCGATGAGCCGCTGGTAGTGGTTACAGAGCATGCTATTA
CCAACCTTCACCAAAGCTGAGATGGCACTTGAATTCATCGTGAGTTTCCTTGACAAGATGCGTGTGCTGTCA
GTGTCACCAAAATATTTCGGATCTTCTGACCTATGTTGACTGCTACGTCGGTGTGTCTGCTCGTCAGGCTTT
AAACAATTTTCAGAAACAAGTGCCTGTGATTACACCTACTAGGCAGACGATGTATGTGCACTCGATACAAG
CGGCCTTGAAAGCTTTAGAAAAGTGGGAGATTGATCTGAGAGTGGCTCAAACGTTGCTGCCTACGAACGTT
CCGATTGGAGAAGTCTCTTGTCCAATGCAGTCGGTAGTGAAACTGCTGGATGATCAGCTGCCAGATGACAG
CCTGATACGGAGGTATCCCAAGGAAGCCGCGCTCGCTTTGGCTAAACGAAACGGGGGAATACAATGGATGG
ACGTATCAGAAGGCACCGTGATGAACGAGGCTGTCAACGCTGTTGCAGCTAGTGCCTGGCACCTTCAGCA
TCAGCCCCACCCTTAGAAGAGAAGTCAAAGTTAACCGAACAAGCGATGGATCTCGTGACCGCGGCTGAGCC
TGAGATAATTGCCTCACTCGCGCCAGTTCCCGCACCCGCTGTTTGCCATACCACCTAAACCAGCAGATTATA
ATGTGCGTACTCTGAGGATCGACGAGGCCACTTGGCTGCGAATGATTCCAAAATCAATGAACACACCTTTT
CAAATCCAGGTGACTGATAACACAGGAATAATTGGCATCTCAATTTGAGGGGGGGGACTCGTGTAGTGAA

Figure 2-2

TCTGGACCAAATCGCTCCGATGCGGTTTGTATTAGATCTAGGGGGAAAGAGTTATAAAGAGACGAGCTGGG
ATCCAAACGGCAAGAAGGTCGGATTCATCGTTTTTCAATCGAAGATACCATTCGAACCTTGGACTGCTGCT
TCACAGATCGGTCAAGCCACGGTGGTTAACTATGTCCAACATAACGCTGAAGACAGCTCATTTACCGCGCA
GTCTATCATTGCTACTACCTCTTTGGCTTATAACTATGAGCCTGAGCAGTTGAATAAGACTGACCCTGAGA
TGAATTATTATCTTTTGGCGACCTTTATAGACTCAGCCGCTATAACGCCAACGAATATGACACAGCCTGAT
GTTTGGGATGCCTTGCTGACGATGTCCCCACTATCAGCTGGCGAGGTGACAGTGAAGGGTGCGGTAGTGAG
TGAAGTAGTCCCTGCAGACTTGATAGGTAGCTACACTCCAGAATCCCTAAACGCCCTCACTTCCGAATGATG
CTGCTAGATGCATGATCGATAGAGCTTCGAAGATAGCCGAAGCAATCAAGATTGATGATGATGCTGGACCA
GATGAATATTCCCCAACTCTGTACCAATTCAAGGTCAGCTTGCTATCTCGCAACTCGAACTGGATATGG
TGTGCGAATATTCAACCCTAAAGGGATCCTTTCTAAAATTGCATCTAGGGCAATGCAGGCTTTCATTGGTG
ACCCGAGCACAATCATCACGCAGGCGGCGCCAGTGTTATCAGACAAGAATAATTGGATTGCATTGGCACAG
GGAGTGAAAACCTAGTCTGCGTACTAAAAGTCTATCAGCGGGAGTGAAGACTGCAGTGAGTAAGCTGAGCTC
ATCTGAGTCTATCCAGAATTGGACTCAAGGATTCTTGATAAAGTGTGAGCGCATTTTCCAGCACCAAAGC
CCGATTGTCCGACTAGCGGAGATAGTGGTGAATCGTCTAATCGCCGAGTGAAGCGCGACTCATACGCAGGA
GTGGTCAAACGTGGGTACACACGTTAGGCCGCTCGCCCTGGTGACGCGGGGTAAAGGGATGCAGGCAAATC
ATC (SEQ ID NO:6)

M3:

GCTAAAGTGACCGTGGTCATGGCTTCATTCAAGGGATTCTCCGCCAACACTGTTCCAGTTTCTAAGGCCAA
GCGTGACATATCATCTCTTGCCGCTACTCCTGGACTTCGTTCACAATCCTTCACTCCGTCTGTGGATATGT
CTCAATCGCGTGAATTCCCTCACAAAGGCAATTGAGCAAGGGTCCATGTCTATACCTTATCAGCATGTGAAT
GTACCGAAAGTTGATCGTAAAGTTGTTAGCCTGGTAGTGCGACCTTTCTCTTCAGGTGCTTTCTCTATCTC
TGGAGTGATTTGCGCCAGCCCATGCCTATCTACTAGAGTGTCTACCCAGCTTGAGCAGGCGATGGCTTTTG
TTGCTTCACCTGAGTCTTTCCAGGCTTCCGACGTGCGCAAGCGCTTTGCCATAAAGCCAGGTATGAGCCTC
CAGGATGCCATCACTGCCTTTATTAACCTTTGTGTCCGCGATGCTGAAAATGACGGTGACTCGTCAAACTT
TGACGTTATTGTGGCTGAGATCGAGAGGCTTGCTTCAACCAGCGTGTCCGTCAGGACTGAAGAAGCGAAGG
TTGCTGATGAGGAGCTAATGCTATTCCGGTTAGATCATAGAGGGCCACAGCAGCTGGATGTTTCTGACGCT
AAAGGGATAATGAAGGCTGCTGATATTCAGACAACCTCATGATGTCCATTTGGCACCAGGCGTTGGTAATAT
TGATCCTGAAATCTATAACGAGGGGCGGTTTCATGTTTCATGCAGCACAAGCCACTTGCGGCGGATCAATCGT
ATTTACCTTGAGACTGCGGATTATTTCAAGATTTATCCAACATACGATGAACATGATGGCAGGATGGCT
GACCAAAGCAGTCGGGATTGATACTGTGTACTAAGGACGAGGTATTGGCTGAGCAAACCTATATTTAACT
GGACGCCCCCTGATGACAAGACTGTTTCATCTGTTGGATCGCGATGACGACCACGTTGTTGCCAGATTTACTA
AGGTATTTATAGAGGACGTGGCTCCCGGGCATCATGCTGCTCAAAGATCGGGACAACGCTCTGTGCTTGAT
GACCTATATGCGAATACGCAAGTGATTTCCATTACTTCTGCTGCTTTAAAGTGGGTGGTCAAGCACGGCGT
ATCTGATGGAATCGTGAACAGGAAGAATGTCAAAGTGTGTGTTGGTTTTGACCCCTGTACACCTTGTCTA
CACATAACGGGGTGTCTTATGTGCCCTGCTGATGGACGAAAACTCTCTGTGCTGAACAGTGCGTGTGCT
ATGACGTTACGCTCACTCATGAAGACCGGACGCGACGTTGATGCACACAGAGCTTTTCAGCGAGTCCTCTC
TCAAGGATACACATCGCTAATGTGCTACTATCATCCTTCACGGAAGTTGGCATATGGTGAGGTGCTCTTTC
TAGAACGATCCAATGACGTGACAGATGGGATCAAGCTTCAGTTGGACGCATCTAGACAGTGTCATGAATGT
CCTGTGTTGCAGCAGAAAGTGTTGAGTTAGAGAAACAGATTATTATGCAGAAGTCAATCCAGTCAGACCC
TACCCAGTGGCGCTGCAACCATTGTTGTCTCAGTTGCGTGAGTTGTCTAGTGAAGTTACTAGGCTACAGA
TGGAGTTGAGTCGAGCTCAGTCCCTGAATGCTCAGTTGGAGGCGGATGTCAAGTCAGCTCAATCATGTAGC
TTGGATATGTATCTGAGACACCACACTTGCAATTAATGGTCATGCTAAAGAAGATGAATTGCTTGACGCTGT
GCGTGTGCGCGCGGATGTGAGGAGAGAAAATCATGGAAAAGAGGAGTGAAGTGAGACAAGGTTGGTGCGAAC
GTATTTCTAAGGAAGCAGCTGCCAAATGTCAAACCTGTTATTGATGACCTGACTTTGATGAATGGAAAGCAA
GCACAAGAGATAACAGAATTACGTGATTCGGCTGAAAAATATGAGAAACAGATTGCAGAGCTGGTGAGTAC
CATCACCCAAAACAGATAACGTATCAGCAAGAGCTACAAGCCTTGGTAGCGAAAAATGTGGAATTGGACG
CGTTGAATCAGCGTCAGGCTAAGTCTTTGCGTATTACTCCCTCTCTTCTATCAGCCACTCCTATCGATTCA
GTTGATGATGTTGCTGACTTAATTGATTTCTCTGTTCCAACCTGATGAGTTGTAAATAATCCGTGATGCAGT
GTTGCCCTAATCCCTTAAGCCTTCCCGACCCCCATTCATC (SEQ ID NO:7)

Figure 3-1

L1:

GCTACACGTTCCACGACAATGTCATCCATGATACTGACTCAGTTTGGACCGTTCATTGAGAGCATTTCAGG
TATCACTGATCAATCGAATGACGTGTTTGAAGATGCAGCAAAAGCATTCTCTATGTTTACTCGCAGCGATG
TCTACAAGGCGCTGGATGAAATACCTTTCTCTGATGATGCGATGCTTCCAATCCCTCCAACCTATATATACG
AAACCATCTCACGATTTCATATTATTACATTGATGCTCTAAACCGTGTGCGTCGCAAAACATATCAGGGCCC
TGATGACGTGTACGTACCTAATTGTTCTATTGTTGAATTGCTGGAGCCACATGAGACTCTGACATCTTATG
GGCGGTTGTCCGAGGCCATCGAGAATCGTGCCAAGGATGGGGACAGCCAAGCCAGAATCGCCACAACGTAT
GGTAGAATCGCTGAATCTCAAGCTCGACAGATTAAGGCTCCATTGGAGAAGTTTGTGTTGGCACTATTAGT
GGCCGAAGCAGGGGGGTCTTTATATGATCCAGTTTTTGCAGAAGTATGATGAGATTCCAGATCTATCGCATA
ATTGCCCTTTATGGTGTTTTAGAGAGATCTGTGCTCACATATCTGGTCCATTACCAGATCGGGCACCTTAT
CTTTACTTATCTGCAGGGGTTTTCTGGTTAATGTCACCACGAATGACGTCTGCAATCCCTCCGCTACTATC
CGATCTTGTTAATTTAGCTATTTTGCAACAACTGCGGGTTTAGATCCATCATTAGTGAAATTGGGAGTAC
AGATATGCCTTCATGCAGCAGCTAGCTCAAGTTATGCATGGTTTTATCTTAAAGACTAAGICTATTTTTCT
CAAAACACGTTGCACAGTATGTATGAATCTCTAGAAGGGGGATACTGTCCTAATCTTGAATGGTTAGAGCC
TAGATCAGACTATAAGTTCATGTACATGGGAGTCATGCCATTGTCCGCTAAGTATGCTAGGTCGGCGCCGT
CCAATGATAAGAAAGCGCGGGAACCTTGGCGAGAAATATGGACTGAGCTCAGTCGTCGGTGAGCTTCGTA
CGGACAAAGACGTATGTTAAACATGACTTTGCTTCAGTGAGGTACATTTCGTGACGCTATGGCATGTACTAG
CGGTATTTTCTTGGTAAGAACACCCACCGAAACGGTATTGCAAGAATATACGCAGAGTCCGGAGATTAAGG
TTCCCATTTCCCGAGAAAGACTGGACAGGCCCAATAGGTGAAATCAGAATTCTAAAAGATACAACAAGTTCC
ATCGCGCGTTACTTATATAGAACATGGTACTTGGCAGCGGCGAGAATGGCGGCTCAACCACGTACGTGGGA
TCCATTGTTTCAAGCGATTATGAGATCTCAATACGTGACAGCTAGGGGTGGATCTGGCGCAGCACTCCGCG
AATCTTTGTATGCAATCAATGTGTCGTTACCTGATTTCAAGGGCTTACCAGTGAAGGCAGCAACTAAGATA
TTCCAGGCGGCACAATTAGCGAACTTGCCGTTCTCCACACATCAGTGGCTATACTAGCTGACACTTCAAT
GGGATTGCGAAATCAGGTGCAGAGGCGGCCACGATCCATTATGCCATTAAATGTGCCCCAGCAGCAGGTTT
CGGCGCCCCATACATTGACAGCGGATTACATTAACCTACCACATGAATCTATCAACCACGICTGGTAGTGCG
GTCATTGAGAAGGTGATTCCTTTAGGTGTATACGCTTCGAGCCCTCCTAACCAGTCGATCAACATTGACAT
ATCTGCGTGTGACGCTAGTATTACTTGGGATTTCTTTCTGTGTCAGTGATTATGGCGGCTATACACGAAGGTG
TCGCTAGTAGCTCCATTGGAAAACCATTTATGGGGGTTCTTGCATCCATTGTAAATGATGAGTCTGTCGTT
GGAGTGAGAGCTGCTAGGCCGATATCGGGAATGCAGAACATGATTTCAGCATCTATCGAACTATATAAACG
TGGATTTTTCATATAGAGTAAACGATTCTTTTTCTCCAGGTAACGATTTTACTCATATGACTACCACTTTCC
CGTCAGGTTCAACAGCCACCTCTACTGAGCATACTGCTAATAATAGTACGATGATGGAACTTTCTCTGACA
GTATGGGGACCCGAACATACTGACGACCCTGACGTCTTACGTTTAAATGAAGTCTTTAACTATTCAAAGGAA
TTACGTATGTCAAGGTGATGATGGATTAATGATTATCGATGGGACTACTGCTGGTAAGGTGAACAGTGAAA
CTATTTCAGAAGATGCTAGAATTAATCTCAAAATATGCTGAGGAATTCGGATGGAAATATGACATACCGTAC
GATGGGACTGCCGAATACTTAAAGCTATACTTCATATTTGGCTGTGCAATTCCAAATCTTAGTCGCCATCC
AATCGTGGGGAAAGAACGGGCGAATTCTTCAGCAGAGGAGCCATGGCCAGCAATTCTAGATCAGATTATGG
GTGTCTTCTTTAATGGTGTTCATGATGGGTACAGTGGCAGCGGTGGATACGTTATTCAITGGGCTCTATGC
TGTGCTTTCTCACGTCAAAGAACAATGATTGGTGAGAGCGTGGGTACCTTCAATATCCTATGTGGTCTTT
TGTCTACTGGGGATTACCACTGGTTAAAGCGTTTGGGTGAGACCCATGGATATTTTCTTGGTACATGCCTA
CTGGAGATCTGGGAATGTATAGTTGGATTAGCTTGATACGCCCTCTGATGACAAGATGGATGGTGGCTAAT
GGTTACGTAACTGACAGATGCTCACCCGTATTTCGGGAACGCAGATTATCGCAGGTGTTTCAATGAACCTAA
ACTATATCAAGGTTATTATATGGCACAATTGCCAGGAATCCTAAGAAGTCTGGACGAGCGGCCCCCTCGGG
AGGTAAGAGAACAATTCCTCAGGCATTATCCGACTATCTACTGCAAAATCCAGAGCTGAAGTCACGTGTG
CTACGTGGTTCGTAGTGAGTGGGAGAAATATGGAGCGGGGATAATTCACAATCCTCCGTCATTATTTCGATGT
GCCCCATAAATGGTATCAGGGTGCGCAAGAGGCAGCAATCGCTACGAGAGAAGAGCTGGCAGAAATGGATG
AGACATTAATGCGCGCTCGAAGGCACAGATATTCGAGCTTTTCAAAGTTATTAGAGGCGIATCTGCTCGTG
AAATGGCGAATGTGCGAGGGCCCGCGAACCGTCGGTGGATTTGCGATTACCATTATGTGCGGGTATTGACCC
ATTAAACTCAGATCCTTTTCTCAAGATGGTAAGCGTTGGACCAATGCTCCAGAGTACGAGAAAGTACTTTG
CTCAGACACTATTTCATGGCAAAGACGGTGTGCGGTCTTGACGTTAACGCGATTGATAGCGCGTTATTACGA
CTGCGAACATTAGGTGCTGATAAGAAAGCATTAAACGGCGCAGTTATTAATGGTGGGGCTTCAGGAGTCAGA
AGCGGACGCATTGGCCGGGAAGATAATGCTACAGGATGTGAATACTGTGCAATTAGCCAGAGTGGTTAACT
TAGCTGTGCCAGATACTTGGATGTCGTTAGACTTTGACTCTATGTTCAAACACCACGTCAAGCTGCTTCCC
AAAGATGGACGTCATCTAAATACTGATATTCCTCCTCGAATGGGATGCTTACGGGCCATTTTACGATTCTT

Figure 3-2

AGGTGCCGGAATGGTAATGACTGCGACTGGAGTTGCTGTGACATCTATCTGGAGGATATAACATGGCGGTG
GTCGGTCACTTGGACAGAGATTCATGACTTGGATGCGACAGGAAGGACGGTCAGCGTGAGTCTACCATGGG
TCGTGGTGCGTCAACTCATC (SEQ ID NO:8)

L2:

GCTAAATGGCGCGATGGCGAACGTTTGGGGGGTGAGACTTGCAGACTCGTTATCTTCACCCACTATTGAGA
CACGAACGCGTCAGTATACCTTACACGATCTTTGCTCAGACCTAGATGCTAATCCGGGGAGGGAACCGTGG
AAACCTCTGCGTAATCAGCGTACTAATAATATTGTGGCTGTGCAATTATTCAGACCATTCAGGGTTTAGT
TTTAGATAACCCAGCTTTATGGATTTCCAGGAGCATTTGATGACTGGGAGCGATTTCATGAGAGAGAAGCTGC
GTGTGCTAAAGTATGAAGTATTGCGCATCTATCCAATCAGCAACTATAGCAATGAACATGTCAACGTCTTC
GTGGCCAATGCTTTGGTGGGCGCTTTCCTGTGCAATCAAGCTTCTATGACCTGCTACCGTTGTTGATAAT
TAATGACACTATGATTGGTGATCTACTTGGCACGGGGGCATCGCTATCACAGTTCTTTCAATCTCATGGAG
ATGTGCTGGAAGTCGCAGCTGGTCGTAAGTATCTGCAGATGGAAACTACTCCAACGATGACGATGATCCT
CCATTATTTGCGAAAGACCTGTCAGATTATGCTAAAGCATTTCTACAGTGACACATATGAAGTGTTGGACAG
GTTCTTTTGGACGCATGACTCTTCAGCGGGGGTCTTAGTGCAATTATGATAAGCCAACGAATGGTCATCACT
ATCTGCTGGGTACTTTGACTCAGATGGTCAGTGCACCTCCTTATATTATTAACGCTACTGACGCAATGTTG
CTTGAATCCTGTCTAGAACAGTTCTCAGCTAATGTGCGTGCGAGACCTGCGCAACCCGTTACACGCTTAGA
CCAATGCTATCATTTAAGATGGGGAGCACAATATGTAGGAGAAGATTCAGTGACATATCGGTTGGGGGTGT
TATCCTTGCTGGCTACCAATGGATATCAATTAGCTAGACCGATTCCAAGACAGTTGACGAATCGATGGTTG
TCGAGCTTTGTGAGTCAAATTATGTCTGACGGCGTCAACGAGACTCCACTGTGGCCCCAAGAAAGGTATGT
GCAGATCGCTTATGATTCACCATCCGTTGTTGATGGGGCTACGCAATATGGCTATGTCAGGAAGAATCAAC
TCAGACTCGGCATGAGAATATCGGCGCTGCAATCGCTGAGTGATACGCCCTCGCCGGTACAGTGGCTTCCA
CAATACACCATCCACCAGGCAGCGATGGACGAAGGCGATCTGATGGTTAGTCGGCTTACGCAACTCCCGTT
ACGTCCTGATTATGGTAATATCTGGGTGCGCGATGCGCTATCCTATTATGTGGACTACAATCGGAGTCATC
GAGTCGTGCTTTCATCGGAACTTCCTCAGCTTCGGGACACATATTTTGATGGCGATGAACAGTATGGGCGC
AGCCTGTTCTCACTAGCTCGTAAGATTGGTGACCGCTCGTTAGTGAAAGATACGGCTGTCTTGAAGCACGC
TTACCAAGCCATCGATCCAAATACTGGTAAGCAGTATCTGAGATCTCGGCAATCTGTGCGCATATTTTGGTG
CATCAGCGGGTCATTCTGGTGCCGACCAGCCGTTAGTCATAGAGCCCTGGATTCAAGGGAAAATCAGTGGT
GTGCCGCCACCCTCCTCAGTGCGACAGTTCGGCTATGATGTTGCCCGTGGCGCGATCGTCGATCTGGCGAG
ACCATTTCTTCTGGAGATTATCAATTTGTCTATTTCGGATGTTGACCAGGTGGTCGATGGCCATGACGATC
TGAGTATATCATCTGGACTGGTGGAGAGCCTTTTGTCTTCATGCATGCACGCCACAGCACCCGGGGGCTCA
TTTGTTGTTAAGATAAATTTTCCGACTAGACCCGATGGCACTACATCGAACAGAAGATCTTGCCCAATAT
TACGTCATACATGTTGATCAAGCCTTTCGTACCAACAACGTGCAATTGTTCTTCGTGCTTTTCGGTGTGC
ATCAACACTCATCACTTACTTGGACATCTGGAGTGACTTCTTCTTGGTGGACCATTTTTATCGTTATGAG
ACTTTATCTACGATCTCACGACAATTGCCGTCTTTTGGGTATGTTGATGATGGGTCTTCCGTGACTGGTAT
CGAGACAATTAGTATTGAGAACCCTGGCTTCTCGAATATGACCCAGGCCGCTCGCATTGGTATCTCAGGAT
TGTGTGCTAATGTAGGTAACGCGCGTAAGTCCATTGCCATTTACGAATCTCATGGGGCCAGAGTATTAAC
ATCACATCAAGGAGATCTCCGGCATCAGCTAGAAGAAAGTCTAGGTTGCGATATTTGCCATTAATAGACCC
TAGGTCGTTAGAGGTACAGGCGCGCACTATTCTGCCAGCTGATCCAGTGTTATTTGAAAACGTGAGCGGAG
CGTCACCCCATGTTTGTCTGACAATGATGTACAACCTTCGAAGTGTCGTCAGCGGTATATGATGGAGACGTT
GTGCTAGATCTTGGGACGGGACCAGAGGCTAAAATCCTTGAAGTATACCCGCAACCTCTCCAGTCACATG
CGTGGACATACGGCCTACAGCGCAGCCTAGTGGATGTTGGAACGTTTCGTACCACGTTCTTGGAGTTAGATT
ATTTGAGCGATGGATGGATCACTGGGGTGCGTGGGGACATAGTTACTTGTATGTTATCTTTGGGGGCCGCT
GCCGCTGGAAAATCAATGACTTTTGACGCTGCGTTTCAGCAATTAATCAAAGTATTATCCAAGAGTACGGC
TAATGTTGTGCTGGTGCAGGTTAACTGCCCTACAGACGTGGTGAGGAGCATTAAGGGCTACCTAGAGATAG
ATTCGACTAACAAGAGGTATAGGTTCCCCAAATTTGGTTCGAGACGAGCCGTACTCTGACATGGATGCGCTG
GAGAAAATATGTCGTACCGCCTGGCCAACTGCTCAATTACCTGGGTTCATTGTCATACGACTTGCGGTG
GACTAGACTGGCATTATTAGAGTCCACGACATTGAGTAGCGCGTCGATTAGAATTGCTGAGCTGATGTATA
AATACATGCCTATTATGAGGATTGATATTCATGGACTACCCATGGAAAAGCGAGGTAACCTTCATAGTGGGG
CAGAACTGCTCATTAGTAATCCCTGGTTTTAATGCGCAGGATGTCTTTAACTGTTATTTCAATTCCGCCCT
CGCTTTCTCGACTGAAGATGTCAATGCTGCGATGATTCCCCAAGTGTCTGCGCAGTTTGATGCGACTAAGG
GTGAGTGGACGTTGGATATGGTCTTCTCCGACGCAGGAATCTATACCATGCAGGCTCTAGTGGGATCTAAT

Figure 3-3

GCTAATCCAGTCTCTTTGGGTTCCCTTTGTAGTTGATTCTCCAGATGTAGATATAACTGACGCTTGGCCAGC
TCAGTTAGACTTTACGATCGCGGGAAGTATGTCGATATAACAGTTAATCCTTATTACCGTCTGATGACCT
TTGTAAGGATCGATGGACAGTGGCAGATTGCCAATCCAGACAAATTTCAATTCTTTTCGTCGGCGTCTGGG
ACGTTAGTGATGAACGTCAAATTAGATATCGCAGATAAATATCTACTATACTATATACGAGATGTCCAGTC
TCGAGATGTTGGCTTTTACATTCAGCATCCACTTCAACTTTTGAATACGATCACATTGCCAACCAACGAGG
ACCTTTTTCTGAGCGCACCTGACATGCGAGAGTGGGCAGTTAAGGAAAGCGGTAACACGATATGTATACTC
AATAGTCAAGGGTTTGTGCTACCTCAAGATTGGGATGTGTTAACAGATAACCATAAGTTGGTCCCCATCGAT
ACCCACATACATTGTGCCACCGGGTGATTATACCTTGACTCCTCTGTAACCTCACTGTCCCTCGTGAGCGCG
CCTAATTCATC (SEQ ID NO:9)

L3:

GCTAATCGTCAGGATGAAGCGGATTCCAAGGAAGACAAAGGGCAAATCCAGCGGAAAGGGCAATGACTCAA
CAGAGAGAGCGGACGATGGCTCGAGCCAATTAAGAGACAAGCAAAACAATAAGGCTGGCCCCGCCACTACG
GAGCCTGGCACATCCAACCGAGAGCAATACAAAGCTCGACCAGGTATTGCATCTGTGCAGAGGGGCCACTGA
AAGTGCAGAAATGCCCATGAAGAATAATGACGAAGGGACGCCAGATAAGAAAGGAAATACTAAGGGCGACC
TAGTTAATGAGCATAGTGAGGCTAAAGACGAGGCGGATGAAGCGACGAAGAAGCAGGCAAAGGATACAGAC
AAAAGTAAAGCGCAAGTCACATATTCAGACACTGGTATCAATAATGCTAATGAACTGTCAAGATCTGGGAA
TGTGGATAATGAGGGTGGAAGTAATCAGAAGCCGATGTCTACCAGAATAGCTGAGGCAACGTCTGCTATAG
TGTCGAAACATCCTGCGCGTGTTGGGCTGCCACCTACCGCTAGCAGTGGTTCATGGGTATCAGTGCCATGTC
TGTTCTGCAGTCCTGTTTGTGCTCTTTAGACCTAGATGCCACGTCGCCTCACATGGTTTGCATGGTAACAT
GACATTAACATCGAGTGATATCCAGCGACATATAACTGAGTTCATCAGCTCATGGCAAAATCATCCTATTG
TTCAAGTTTCGGCTGATGTGCAAAATAAGAAAAGTCTCAATTGCTTCACGCTGACACTCCTCGACTCGTC
ACTTGGGATGCTGGTTTGTGTACTTCATTCAAAATCGTCCCGATTGTGCCAGCTCAGGTGCCGCAGGATGT
ACTGGCCTATACGTTTTTACCTCTTCATACGCTATCCAATCACCGTTTCCAGAGGCGGCAGTGTCTAGGA
TTGTGGTGCATACGAGATGGGCATCTAATGTTGACTTTGACCGAGACTCGTCTGTTCATCATGGCGCCACCT
ACAGAAAACAATATCCATTTGTTTAAACAGTTACTAAATACTGAAACCCTGTCTGTAAGGGGGGCTAATCC
GCTAATGTTTCAGGGCGAATGTGTTGCATATGTTGCTAGAGTTCGTATTAGATAACTTGTATCTGAACAGAC
ATACGGGATTCTCTCAAGACCACACGCCATTTACTGAGGGTGCTAATTTGCGTTCACCTCCTGGCCCCGAT
GCTGAGAAATGGTACTCGATTATGTATCCAACGCGCATGGGAACGCCGAATGTATCCAAAATATGTAATTT
CGTCGCCTCTTGTGTGCGAAATCGGGTTGGACGGTTTGATCGAGCACAGATGATGAACGGAGCTATGTGAG
AGTGGGTGGATGTCTTCGAGACTTCAGACGCGCTAACCGTCTCCATTCGAGGTTCGATGGATGGCTAGACTA
GCTCGCATGAACATAAATCCAACAGAGATCGAATGGGCATTGACTGAATGTGCACAAGGATATGTGACTGT
CACAAAGTCCTTACGCTCCTAGCGTAAATAGATTGATGCCCTATCGTATCTCCAACGCTGAGCGGCAAATAT
CACAGATAATCAGGATCATGAACATTGGCAATAACGCGACGGTGATACAACCTGTTCTGCAAGATATTTTCG
GTACTCCTTCAACGCATATCACCCTCCAAATAGATCCAATATTATTTCCAACACTATGTCAACAGTCTC
GGAGTCTACTACTCAGACCCCTCAGCCCCGCGTCTCAATTTTGGGTAAACTACGACCAAGCAACTCAGATT
TTTCTAGTTTTTAGAGTCGCGTTGGCTGGATGGCTTTATAATGGGGTTGTGACGACGGTGATTGATGATAGT
TCATATCCAAAAGACGGCGGCAGCGTGACCTCACTTGAAAATCTGTGGGATTTCTTCATCCTTGCGCTTGC
TCTACCACTGACAACTGACCCCTGTGCACCTGTGAAAGCATTTCATGACCCTAGCCAAACATGATGGTTGGTT
TCGAGACAATCCCTATGGATAATCAGATCTATACTCAATCGAGACGCGGAGTGCTTTCTCAACGCCTCAC
ACGTGGCCACGATGCTTTATGAACATCCAGTTAATTTCTCCAATCGACGCTCCCATCTTGCGACAGTGGGC
TGAAATTATTCATAGATACTGGCCTAACCTTCACAGATTTCGTTATGGTGCACCGAACGTTTTTCGGCTCGG
CAAATTTGTTCACTCCACCTGAGGTGCTGTTATTGCCAATCGATCATCAACCAGCTAATGTAACAACGCCA
ACGCTGGACTTCACCAATGAGTTAACTAATTGGCGCGCTCGTGTCTGTGAGCTTATGAAGAATCTCGTTGA
TAACCAAAGATATCAACCTGGATGGACACAAAGTCTAGTCTCGTCAATGCGCGGAACGCTAGACAAATTGA
AGTTGATTAAATCGATGACACCAATGTATCTGCAACAGCTGGCTCCGGTAGAGTTAGCAGTGATAGCTCCC
ATGTTGCCTTTTCCACCTTTCCAGGTGCCATACGTCCGTCTCGATCGTGACAGAGTTCCAACAATGGTTGG
AGTAACACGACATTCACGAGATACTATTACTCAGCCGGCGCTATCGCTGTGACAACCAATACTACTGTTG
GCGTGCCACTAGCTCTAGACGCGAGGGCTATCACCGTTGCGCTGTTGTGAGGAAATATCCGCCGGATTTG
GTGACAAATGTATGGTACGCTGATGCCATTTACCCAATGTATGCAGACACGGAGGTGTTCTCTAATCTTCA
GAGAGACATGATTACCTGCGAGGCCGTGCAGACATTAGTGACTCTGGTGGCGCAAATATCAGAGACCCAGT
ATCCTGTAGATAGGTATCTTGATTGGATCCCATCACTGAGAGCATCGGCGGCGACGGCGGCGACATTTGCT

Figure 3-4

GAGTGGGTTAATACTTCAATGAAGACGGCGTTTGATTTGTCTGATATGCTGTTAGAGCCTCTCCTAAGCGG
TGATCCGAGGATGACTCAACTAGCGATTTCAGTATCAGCAGTACAATGGCAGAACGTTTAATATCATACTG
AAATGCCAGGTTCAGTAATTGCTGACTGCGTTCAATTAACAGCAGAAGTCTTTAATCACGAATATAACCTG
TTTGGGATTGCGCGGGGTGATATCATCATTTGGCCGTGTTTCAGTCGACACATTTGTGGTCACCGCTGGCTCC
TCCACCTGACCTGGTGTGTTGATCGTGATACCCCTGGTGTTCACATCTTCGGACGAGATTGCCGTATATCGT
TTGGAATGAATGGCGCCGCGCCAATGATTAGAGATGAGACTGGACTGATGGTGCCTTTTGAAGGAAATTGG
ATTTTCCCCTGGCGCTTTGGCAAATGAATACACGATATTTTAATCAACAGTTCGACGCGTGGATTAAGAC
AGGAGAGTTGCGAATCCGCATTGAGATGGGCGCGTATCCATATATGTTGCATTACTATGATCCACGTCAGT
ACGCTAATGCATGGAATTTAACATCCGCCTGGCTTGAAGAAATTACGCCGACGAGCATCCCATCCGTGCCT
TTCATGGTGCCCATTTCAAGTGATCATGACATTTCTCTGCCCCAGCTGTCCAATATATCATTTCAACTGA
ATATAATGATCGGTCTCTGTTCTGCACTAACTCATCATCTCCCCAAACCATCGCTGGACCAGACAAACACA
TTCCAGTTGAGAGATATAACATTCTGACCAACCCCGACGCTCCACCCACGCAGATACAACTGCCTGAAGTC
GTTGACTTGTACAACGTCGTCACACGCTATGCGTATGAGACTCCGCCTATTACCGCTGTTGTTATGGGTGT
TCCTTGATCCTCATCCTCCCAACAGGTGCTAGAGCATTGCGCTCAATGCTAGTTGGGCCGATTCATC
(SEQ ID NO:10)

Figure 4

[1:

MDPRLREEVVRLIIALTSDNGASLSKGLSRVSALEKTSQIHSDTILRITQGLDDANKRIIALEQSRDDL
ASVSDAQLAISRLESSIGALQTVVNGLDSSVTQLGARVGQLETGLAELRVDHDNLVARVDTAERNIGSLTT
ELSTLTLRVTSIQADFESRISTLERTAVTSAGAPLSIRNNRMTMGLNDGLTSLGNNLAIRLPGNTGLNIQN
GGLQFRFNTDQFQIVNNNLTLKTTVFDSINSRIGATEQSYVASAVTPLRLNSSTKVLDMLIDSSTLEINSS
GQLTVRSTSPNLRYPIADVSGGIGMSPNYRFRQSMWIGIVSYSGSGLNWRVQVNSDIFIVDDYIHICLP
AFDGEFIADGGDLSLNFVTGLLPPLLTGDTEPAFHNDVVITYGAQTVAIGLSSGGAPQYMSKNLWVEQWQD
GVLRLRVEGGGSITHSNSKWPAMTVSYPRSFT (SEQ ID NO:11)

[2:

MARAAFLFKTVGFGGLQNVPINDELSSHLLRAGNSPWQLTQFLDWISLGRGLATSALVPTAGSRYYQMSCL
LSGTLQIPFRPNHRWGDIFRLRLVWSAPTLDGLVVAPPQVLAQPALQAQADRVYDCDDYPFLARDPRFKHR
VYQQLSAVTLLNLTGFGPISYVRVDEDMWSGDVNQLLMNYFGHTFAEIAYTLCQASANRPWEYDGT
YARMTQIVLSLFWLSYVGVHQQNTYRTFYFQCNRGDAAEVWILSCSLNHSQAQIRPGNRS
LFLVMPTSPDWNMDVNLISSTLTGCLCSGSQPLIDNNSVPAVSRNIHGWTRAGNQLHGFQV
RRMVTEFCDRLLRDRDGMVTQAQQNQVEALADQTQQFKRDKLETWAREDDQYNQAH
PNSTMFRTKPFNAQWGRGNTGATSAAIAALI (SEQ ID NO:12)

[NS:

MASSLRAAISIKIKRDDVGQQVCPNYVMLRSSVTTKVVRNVVEYQIRTGGFFSCLAMLRPLQYAKRERLLGQ
RNLERISTRDILQTRDLHSLCMPTPDAPMSNHQASTMRELICSYFKVDHADGLKYIPMDERYSPSS
LARLFTMGMAGLHITTEPSYKRVPIMHLAADLDCMTLALPYMITLDGDTVVPVAPTLSAEQLLDDGLKGLACMDMD
VRWTRIAGRLVIRVWTLHAASTSCIARRQQKPSVCLRHLC (SEQ ID NO:13)

MASSLRAAISIKIKRDDVGQQVCPNYVMLRSSVTTKVVRNVVEYQIRTGGFFSCLAMLRPLQYAKRERLLGQ
RNLERISTRDILQTRDLHSLCMPTPDAPMSNHQASTMRELICSYFKVDHADGLKYIPMDERYSPSS
LARLFTMGMAGLHITTEPSYKRVPIMHLAADLDCMTLALPYMITLDGDTVVPVAPTLSAEQLLDDGLKGLACMDIS
YGCEVDANSRPAGDQSMDSRCINELYCEETAEAICVLKTCLVLNCMQFKLEMDDLHNAAELDKIQMMIP
FSERVFRMASSFATIDAQCFRFCVMMKDKNLKIDMRETTTLWTRRSASDDSVATSSLSISLDRGRWVAADAS
DARLLVFPIRV (SEQ ID NO:14)

[3:

MEVCLPNGHQVVDLINNAFEGRVSIYSAQEGWDKTI SAQPDMMVCGGAVVCMHCLGVVGS
LQQRKLKHLPHHRCNQQIRHQDYVDVQFADRVTAHWKRGMLS FVAQMHEMMNDVSPDDLDRV
RTEGGSLVELNRLQVDPNSMFRSIHSSWTDPLQVVDDLDTKLDQYWTALNLMIDSSDLIPNFM
MRDP SHAFNGVKLKG DARQTQFSRTFDSRSSLEWGMVYDYSELHDPSKGRAYRKELVTPARDFG
HFGLSHYSRATTPILGKMPAVFSGMLTGNCKMYPFIKGTAKLKTVRKLVEAVNHAWGVEKIRYALG
PPGMTGWYNRTMQQAPIVLT PAALTMFPDTIKFGDLNYPVMIGDPMILG (SEQ ID NO:15)

Figure 5

p2:

MAYIAVPAVVDSRSSEAIGLLESEFGVDAGADANDVSYQDHDYVLDQLQYMLDGYEAGDVIDALVHKNWLHH
SVYCLLPKSQLLEYWKSNPSPAI PDNVDRRLRKRLMLKKDLRKDDDEYNQLARAFKISDVYAPLISSTTSPM
TMIQNLNRGEIVYTTTDRVIGARILLYAPRKYYASTLSFTMTKCIIPFGKEVGRVPHSRFNVGTFPSIATP
KCFVMSGVDIESIPNEFIKLFYQRVKSVHANILNDISPQIVSDMINRKRLRVHTPSDRRAAQLMHLPYHVK
RGASHVDVYKVDVVDMLFEVVVDVADGLRNVSRKLTMTHTVPVCILEMLGIEIADYCIHQEDGMLTDWFLLLT
MLSDGLTDRRTHCQYLINPSSVPPDVILNISITGFINRHTIDVMPDIYDFVKPIGAVLPKGSFKSTIMRVL
DSISILGIQIMPRAHVVDSDDEVGEQMEPTFEQAVMEIYKGIAGVDSLDDLIKWVLNSDLIPHDDRLGQLFQ
AFLPLAKDLLAPMARKFYDNSMSEGRLLTFSHADSELLNANYFGHLLRLKIPYITEVNLMIKKNREGGELF
QLVLSYLYKMYATSAQPKWFGSLLRLLICPWLHMEKLIGEADPASTSAEIGWHIPREQLMQDGWCGCEDGF
IPYVSIRAPRLVIEELMEKNWGQYHAQVIVTDQLVVGEPRRVSAKAVIKGNHLPVKLVSRFACFTLTAKYE
MRLSCGHSTGRGAAYSARLAFRSDLA (SEQ ID NO:16)

p1:

MGNASSIVQTINVTGDGNVEKPSAETSSTAVPSLSLSPGMLNPGGVPWIAVGDETSVTSPGALRRMTSKDI
PDTAIINTDNSSGAVPSESALVPYIDEPLVVVTEHAITNFTKAEMALEFNREFLDKMRVLSVSPKYSDLLT
YVDCYVGVSARQALNNFQKQVPVITPTRQTMVDSIQAAALKALEKWEIDLRVAQTLLPTNVPIGEVSQPMQ
SVVKLLDDQLPDDSLIRRYPKAAVALAKRNGGIQWMDVSEGTVMNEAVNAVAASALAPSASAPPLEEKS
LTEQAMDLVTAAEPEIIASLAPVPAPVFAIPPKPADYNVRTLRIDEATWLRMIPKSMNTPFQIQVTDNTGT
NWHNLNRGGTRVVNLDQIAPMRFVLDLGGKSYKETSWDPNGKKVGFI VFQSKIPFELWTAASQIGQATVVN
YVQLYAEDSSFTAQSIIATTSLAYNYEPEQLNKTDPEMNYLLATFIDSAAITPTNMTQPDVWDALLTMSP
LSAGEVTVKGAVVSEVVPADLIGSYTPESLNASLPNDAARCMIDRASKIAEAIKIDDDAGPDEYSPNSVPI
QGQLAISQLETGYGVRIENPKGILSKIASRAMQAFIGDPSTIITQAAPVLSDKNNWIALAQGVKTSRLTKS
LSAGVKTAVSKLSSSESIQNWQTQGFLLDKVSAHFPAKPKDCPTSGDSGESSNRRVKRDSYAGVVKRGYTR
(SEQ ID NO:17)

pNS:

MASFKGFSANTVPVSKAKRDISSLAATPGLRSQSFTPSVDMSQSREFLTKAIEQGSMSIPYQHVNVPKVDR
KVVSLVVRPFSSGAFSISGVISPAHAYLLECLPQLEQAMAFVASPESFQASDVAKRFAIKPGMSLQDAITA
FINFVSAMLKMTVTRQNFVDVIVAEIERLASTSVSVRTEEAKVADEELMLFGLDHRGPQQLDVSDAKGIMKA
ADIQTTHDVHLAPGVGNIDPEIYNEGRFMFMQHKPLAADQSYFTLETADYFKIYPTYDEHDGRMADQKQSG
LILCTKDEVLAEQTIFKLDAPDDKT VHLLDRDDHVVARFTKVFIEDVAPGHHAQAQRSGQRSVLDDLYANT
QVISITSAALKWVVKHGVSDGIVNRKNVKVCVGFDPYTLSTHNGVSLCALLMDEKLSVLNSACRMTLRSL
MKTGRDVEDAHRAFORVLSQGYTSLMCYYHPSRKLAYGEVLFLEERSNDVTDGIKLQLDASRQCHECPVLQQK
VVELEKQIIMQKSIQSDPTPVALQPLLSQLRELSSEVTRLQMELSRAQSLNAQLEADVKSQAQSCSLDMYLR
HHTCINGHAKEDELLDVAVRVAPDVRREIMEKRSEVRQGW CERISKEAAAKCQTVIDDLTLMNGKQAQTE
LRDSAKEYEKQIAELVSTITQNTQITYQQELQALVAKNVELDALNQRQAKSLRITPSLLSATPIDSVDDVAD
LIDFSVPTDEL (SEQ ID NO:18)

Figure 6-1

 $\lambda 3$:

MSSMILTQFGPFIESISGITDQSNDFEFDAAKAFSMFTRSDVYKALDEIPFSDDAMLPIPPPTIYTKPSHDS
YYYIDALNRVRRKTYQGPDDVYVPNC SIVELLEPHETLTSYGRLSEAIENRAKDGDSQARIATTYGRIAES
QARQIKAPLEKFVLALLVAEAGGSLYDPVLQKYDEIPDLSHNCPLWCFREICRHISGPLPDRAPYLYLSAG
VFWLMSPRMTSAIPPLLSDLVNLAILQQTAGLDPSLVKLG VQICLHAAASSSYAWFILKTKSIFPQNTLHS
MYESLEGGYCPNLEWLEPRSDYKFMVMGVMPLSAKYARSAPSNDKKARELGEKYGLSSVVGELRKRTKTYV
KHDFASVRYIRDAMACTSGIFLVRTPTETVLQEYTQSPEIKVPI PQKDWTPIGEIRILKDTTSSIARYLY
RTWYLAARMAAQPRTWDP L FQAIMRSQYVTARGGSGAALRESLYAINVSLPDFKGLPVKAATKIFQAAQL
ANLPFSHTSVAILADTSMGLRNQVQRRPRSIMPLNVPQQQVSAPHTLTADYINYHMNLSTTSGSAVIEKVI
PLGVYASSPPNQ SINIDISACDASITWDFFLSVIMAAIHEGVASSSIGKPFMGVPASIVNDES VVG VRAAR
PISGMQNMIOHLSKLYKRGFSYRVNDSFSPGNDFTHTTTTFPSGSTATSTEHTANNSTMMETFLT VWGPEH
TDDPDVLRMLKSLTIQRNYVCQGDDGLMIIDGTTAGKVNSETIQKMLELISKYGEEFGWKYDIAYDGTA EY
LKLYFIFGCRIPNLSRHPIVGKERANSSAEPPWPAILDQIMGVFFNGVHDGLQWQRWIRYSWALCCAFSRQ
RTMIGESVGYLQYPMWSFVYWGLPLVKAFGSDPWIFSWYMPGTGDLGMYSWISLIRPLMTRWMVANGYVTDR
CSPVFGNADYRRCFNELKLYQGYMAQLPRNP KSGRAAPREVREQFTQALSDYLLQNP ELKSRVLRGRSE
WEKYGAGIIHNPPSLFDVPHKWYQGAQEA AIATREELAEMDETLMRARRHRYSSFSKLLEAYLLVKWRMCE
AREPSVDLRLPLCAGIDPLNSDPFLKMVS VGPMLQSTRKYFAQTIFMAKTVSGLDVNAIDSALLRLRTLGA
DKKALTAQLLMVCLQESEADALAGKIMLQDVNTVQLARVVNLAVPDTWMSLDFD SMFKHHVKLLPKDGRHL
NTDIPPRMGWLRAILRFLGAGMVM TATGVAVDIYLEDIHGGGRSLGQRFMTWMRQEGRSA (SEQ ID
NO:19)

 $\lambda 2$:

MANVWGVRLADSLSSPTIETRTRQYTLHDLCSLDLDANPGREPWKPLRNQRTNNIVAVQLFRPLQGLVLDTQ
LYGFPGAFFDWERFMREKLRVLKYEV LRIYPI SNYSNEHVNVFVANALVGAFLSNQAFYDLLPLLIINDTM
IGDLLGTGASLSQFFQSHGDVLEVAAGRKY LQMENYSNDDDDPPLFAKDLSDYAKAFYS DTYEVLDRFFWT
HDSSAGVLVHYDKPTNGHHYLLGTLTQMVSAPPYIIINATDAMLLESCLEQFSANVRARPAQPVTRLDQCYH
LRWGAQYVGEDSLTYRLGVLSLLATNGYQLARPIPRQLTNRWLSS FVSQIMSDGVNETPLWPQERYVQIAY
DSPSVVDGATQYGYVRKNQLRLGMRISALQSLSDTPSPVQWLPQYTIDQAAMDEGDLMVSRLTQLPLRPDY
GNIWVGDALSYVVDYNRSHRVVLSSEL PQLPDTYFDGDEQYGRSLFSLARKIGDRSLVKDTAVLKHAYQAI
DPNTGKEYLRSRQSVAYFGASAGHSGADQPLVIEPWIQ GKISGVPPPSSVRQFGYDVARGAIVDLARPFPS
GDYQFVYSDVDQVVDGHDDLSISSGLVESLLSSCMHATAPGGSFVVKINFPTRPVWHYIEQKILPNITSYM
LIKPFVTNNVELFFVAFGVHQHSSLTWTSGVYFFLVDHFYRYETLSTISRQLPSFGYVDDGSSVTGIETIS
IENPGFSNMTQAARIGISGLCANVGNARKSIAIYESHGARVLTITSRSPASARRKSRLRYLPLIDPRSLE
VQARTILPADPVLFENVSGASPHVCLTMMYNFEVSSAVYDGDVVLDTGTGPEAKILELIPATSPVTCVDIR
PTAQPSGCWNVRTTFLELDYLSDGWITGVRGDIVTCMLSLGAAAAGKSMTFDAAFQQLIKVLSKSTANVVL
VQVNCPTDVVRSIKGYLEIDSTNKRYRFPKFG RDEPYSDMDALEKICRTAWPNCSITWVPLSYDLRWTRLA
LLESTTLSSASIRIAELMYKYPIMRIDIHGLPMEKRGNFIVGQNC SLVIPGFNAQDVFN CYFNSALAFST
EDVNAAMIPQVSAQF DATKGEWTLDMVFSDAGIYTMQALVGSNANPVSLG SFVVDSPDVIDITDAWPAQLDF
TIAGTDVDITVNPYYRLMTFVRIDGQWQIANPDKFQFFSSASGTLVMNVKLDIADKYLLYYIRDVQSRDVG
FYIQHPLQLLNTITLPTNEDLFLSAPDMREWAVKESGNTICILNSQGFVLPQDWDLTDTISWSPSIPTYI
VPPGDYTLTPL (SEQ ID NO:20)

 $\lambda 1$:

MKRI PRKTKGKSSGKGNDSTERADDGSSQLRDKQNNKAGPATTEPGTSNREQYKARPGIASVQRATESAEM
PMKNNDEGTPDKKGNTKGD LVNEHSEAKDEADEATKKQAKD TDKSKAQVTYS DTGINNANELSRSGNV DNE
GGSNQKPMSTRIAEATSAIVSKH PARVGLPPTASSGHGYQCHVCSAVLFSPLDLDAHVASHGLHGNMTLTS
SDIQRHITEF ISSWQNHPIVQVSADVENK KTAQLLHADTPRLVTWDAGLCTSFKIVPIVPAQVPQDVLAYT
FFTSSYAIQSPFPEAAVSRIVVHTRWASNVD FDRDSSVIMAPPTENNIHLFKQLLNTETLSVRGANPLMFR
ANVLHMLLEFVL DNLYLNRHTGFSQDHTPFTEGANLRSLPGPDAEKWYSIMYPTRMGTPNVSKICNFVASC
VRNRVGRFDRAQMMNGAMSEWVDVFETSDALTVSIRGRWMARLARMNINPTEIEWALTECAQGYVTVTSPY
APSVNRLMPYRISNAERQISQIIRIMNIGNNATVIQPV LQDISVLLQRI SPLQIDPTIISNTMSTVSESTT
QTLSPASSILGKL RPSNSDFSSFRVALAGWLYNGVVTVIDDSSYPKDGGSVTSLENLWDEFFILALALPLT

Figure 6-2

TDPCAPVKAFMTLANMMVGFETIPMDNQIYTQSRRASAFSTPHTWPRCFMNIQLISPIDAPILRQWAEIIH
RYWPNPSQIRYGAPNVFGSANLFTPPEVLLLPIDHQPANVTTPTLDFTNELTNWRARVCELMKNLVDNQRY
QPGWTQSLVSSMRGTLDKCLKLIKSMTPMYLQQ LAPVELAVIAPMLPFPPFQVPYVRLDRDRVPTMVGVTRH
SRDTITQPALSLSTTNTTVGVPLALDARAITVALLSGKYPPDLVTNVWYADAIYPMYADTEVFSNLQRDMI
TCEAVQTLVTLVAQISETQYPVDRLDWIPSLRASAATAATFAEWVNTSMKTAFDLSDMLLEPLLSGDPRM
TQLAIQYQQYNGRTFNIIPEMPGSVIADCVQLTAEVFNHEYNLFGIARGDIIIGRVQSTHLWSPLAPPPDL
VFDRDTPGVHIFGRDCRISFGMNGAAPMIRDETGLMVPFEGNWIIFPLALWQMNTYFNQQFDAWIKTGELR
IRIEMGAYPYMLHYDPRQYANAWNLTSAWLEEITPTSIPSVPFMVPISSDHDISSAPAVQYIISTEYNDR
SLFCTNSSSPQTIAGPDKHIPVERYNILTNPDA PPTQIQLP EVVDLYNVVTRYAYETPPITAVVMGVP
(SEQ ID NO:21)

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**REOVIRUSES HAVING MODIFIED
SEQUENCES****CROSS REFERENCE TO RELATED
APPLICATIONS**

This application is a divisional of U.S. application Ser. No. 12/046,095, filed Mar. 11, 2008, which claims priority under 35 U.S.C. 119(e) to U.S. Application No. 60/894,425 filed on Mar. 12, 2007 and U.S. Application No. 60/989,568 filed on Nov. 21, 2007, all of which are herein incorporated by reference in their entireties.

TECHNICAL FIELD

This invention relates to viruses, and more particularly to reoviruses having modified sequences.

BACKGROUND

The name reovirus derives from an acronym for respiratory and enteric orphan virus, reflecting that the initial isolates came from human respiratory and enteric tracts but were not associated with serious disease. Reoviruses have a double-stranded, segmented RNA genome. The virions measure 60-80 nm in diameter and possess two concentric capsid shells, each of which is icosahedral. The mammalian reovirus genome consists of double-stranded RNA in 10 discrete segments with a total genome size of ~23.5 kbp. The individual RNA segments vary in size.

Three serologically distinct but related types of reovirus have been recovered from mammalian species: type 1 (representative strains include, for example, Lang (T1L)), type 2 (representative strains include, for example, Jones (T2J)) and type 3 (representative strains include, for example, Dearing or Abney (T3D or T3A, respectively)). The three serotypes are easily identifiable on the basis of neutralization and hemagglutinin-inhibition assays (see, for example, Sabin, 1959, *Science*, 130:966; Fields, et al., 1996, *Fundamental Virology*, 3rd Ed., Lippincott-Raven; Rosen, 1960, *Am. J. Hyg.*, 71:242; and Stanley, 1967, *Br. Med. Bull.*, 23:150).

SUMMARY

Provided herein are reoviruses having modified nucleic acid and polypeptide sequences. Sequence modifications include, for example, modifications in one or more of the reovirus genome segments. Also provided are pharmaceutical compositions that include reoviruses having a modified sequence as well as methods of using such reoviruses.

In one aspect, the invention provides a reovirus that has a lambda-3 polypeptide having one or more amino acid modifications; a sigma-3 polypeptide having one or more amino acid modifications; a mu-1 polypeptide having one or more amino acid modifications; and/or a mu-2 polypeptide having one or more amino acid modifications. Such a reovirus can be, for example, non-naturally occurring. In another aspect, the invention provides a reovirus lambda-3 polypeptide having one or more amino acid modifications; a reovirus sigma-3 polypeptide having one or more amino acid modifications; a reovirus mu-1 polypeptide having one or more amino acid modifications; and/or a reovirus mu-2 polypeptide having one or more amino acid modifications.

By way of example, the one or more amino acid modifications in the lambda-3 polypeptide can be a Val at residue 214, an Ala at residue 267, a Thr at residue 557, a Lys at residue 755, a Met at residue 756, a Pro at residue 926, a Pro at residue

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963, a Leu at residue 979, an Arg at residue 1045, a Val at residue 1071, or any combination thereof, numbered relative to GenBank Accession No. M24734.1. It is noted that, when the amino acid sequence is a Val at residue 214 or a Val at residue 1071, the amino acid sequence further includes at least one additional change in the amino acid sequence. In one embodiment, the lambda-3 polypeptide includes the sequence shown in SEQ ID NO:19.

Further by way of example, the one or more amino acid modifications in the sigma-3 polypeptide can be a Leu at residue 14, a Lys at residue 198, or any combination thereof, numbered relative to GenBank Accession No. K02739. It is noted that, when the amino acid sequence is a Leu at residue 14, the amino acid sequence further includes at least one additional change in the amino acid sequence. In one embodiment, the sigma-3 polypeptide includes the sequence shown in SEQ ID NO:15.

Further by way of example, the one or more amino acid modifications in the mu-1 polypeptide can be an Asp at residue 73 numbered relative to GenBank Accession No. M20161.1. In one embodiment, the mu-1 polypeptide includes the sequence shown in SEQ ID NO:17.

Also by way of example, the amino acid modification mu-2 polypeptide can be a Ser at residue 528 numbered relative to GenBank Accession No. AF461684.1. In one embodiment, the mu-2 polypeptide includes the sequence shown in SEQ ID NO:16.

A reovirus as described herein having one or more modifications can further include a reovirus sigma-2 polypeptide. Such a sigma-2 polypeptide can have a Cys at one or more of position 70, 127, 195, 241, 255, 294, 296, or 340, numbered relative to GenBank Accession No. NP_694684.1. In one embodiment, the sigma-2 polypeptide includes the sequence shown in SEQ ID NO:12.

In another aspect, the invention provides a reovirus that has a L1 genome segment having one or more nucleic acid modifications; a S4 genome segment having one or more nucleic acid modifications; a M1 genome segment having one or more nucleic acid modifications; and/or a M2 genome segment having one or more nucleic acid modifications. Such a reovirus can be, for example, non-naturally occurring. In another aspect, the invention provides a L1 genome segment having one or more nucleic acid modifications; a S4 genome segment having one or more nucleic acid modifications; a M1 genome segment having one or more nucleic acid modifications; and/or a M2 genome segment having one or more nucleic acid modifications.

By way of example, the one or more nucleic acid modifications in the L1 genome segment can be a T at position 660, a G at position 817, an A at position 1687, a G at position 2283, an ATG at positions 2284-2286, a C at position 2794, a C at position 2905, a C at position 2953, an A at position 3153, or a G at position 3231, numbered relative to GenBank Accession No. M24734.1. In one embodiment, the L1 genome segment includes the sequence shown in SEQ ID NO:8.

Further by way of example, the one or more nucleic acid modifications in the S4 genome segment can be an A at position 74 and an A at position 624, numbered relative to GenBank Accession No. K02739. In one embodiment, the S4 genome segment includes the sequence shown in SEQ ID NO:4.

Further by way of example, the nucleic acid modification in the M2 genome segment can be a C at position 248, numbered relative to GenBank Accession No. M20161.1. In one embodiment, the M2 genome segment includes the sequence shown in SEQ ID NO:6.

Also by way of example, the nucleic acid modification in the M1 genome segment can be a T at position 1595, numbered relative to GenBank Accession No. AF461684.1. In one embodiment, the M1 genome segment includes the sequence shown in SEQ ID NO:5.

A reovirus as described herein can include any modification or combination of modifications disclosed herein. In some embodiments, a reovirus as described herein is a reassortant. In certain embodiments, a reovirus as described herein includes genomic segments having the sequences shown in SEQ ID NOs:1-10 or the polypeptides shown in SEQ ID NOs:11, 12, and 16-21, and either or both SEQ ID NO:13 or 14. In one embodiment, a reovirus as disclosed herein is identified as IDAC Accession No. 190907-01.

A reovirus as disclosed herein generally exhibits a growth advantage over a reovirus that does not contain a corresponding modification. Representative growth advantages include, but are not limited to, an increased rate of lysis; an increased size of plaque formation; an increased rate of RNA replication; an increased rate of RNA transcription; an increased rate of translation; an increased rate of virus assembly and/or packaging; an increased number of viral progeny; an increased ability of a reovirus to be taken up by a host cell; an increased or enhanced ability to uncoat; enhanced cell lysis or inducement to cell death including apoptosis, necrosis or autophagy; an enhanced ability to infect, lyse and kill human neoplastic cells lines; decreased immunogenicity in mammalian cells; differential susceptibility to interferon sensitivity; decreased toxicity toward the host; enhanced drug interaction; enhanced radiotherapy interaction; or the ability to release effective tumor epitopes.

A reovirus as described herein can be included, along with a pharmaceutically acceptable carrier, in a pharmaceutical composition. Such pharmaceutical compositions can include, for example, one or more chemotherapeutic agents and/or one or more immunosuppressive agents.

In still another aspect, the invention provides for methods of making an improved reovirus. Such methods generally include the steps of modifying the nucleic acid sequence of the reovirus, and selecting one or more improved reoviruses. In some embodiments, the modifying step includes, for example, mutagenizing the reovirus. Representative types of mutagenesis include, without limitation, site-directed mutagenesis and chemical mutagenesis. In other embodiments, the modifying step includes culturing the reovirus in a human cell line.

An improved reovirus made according to the methods disclosed herein can be selected for an increased rate of lysis; an increased size of plaque formation; an increased rate of RNA replication; an increased rate of RNA transcription; an increased rate of translation; an increased rate of virus assembly and/or packaging; an increased number of viral progeny; an increased ability of a reovirus to be taken up by a host cell; an increased or enhanced ability to uncoat; enhanced cell lysis or inducement to cell death including apoptosis, necrosis or autophagy; an enhanced ability to infect, lyse and kill human neoplastic cells lines; decreased immunogenicity in mammalian cells; differential susceptibility to interferon sensitivity; decreased toxicity toward the host; enhanced drug interaction; enhanced radiotherapy interaction; or the ability to release effective tumor epitopes.

In yet another aspect, the invention provides methods of treating a proliferative disorder in a patient. Such methods generally include administering a modified reovirus as described herein or a pharmaceutical composition containing such a modified reovirus to the patient. Typically, the reovirus is administered in an amount effective to cause oncolysis, and

can be administered more than once. Representative routes of administration include, for example, direct injection, intravenously, intravascularly, intrathecally, intramuscularly, subcutaneously, intraperitoneally, topically, orally, rectally, vaginally, nasally, or by inhalation. The methods of treating a proliferative disorder as described herein can be accompanied by one of more procedures such as surgery, chemotherapy, radiation therapy, and immunosuppressive therapy.

In another aspect, the invention provides a kit (or article of manufacture) that includes a reovirus having a modified sequence or any combination of genome segments having a modified sequence as disclosed herein. A kit also can include one or more agents as disclosed herein.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety.

The details of one or more embodiments of the invention are set forth in the accompanying drawings and the description below. Other features, objects, and advantages of the invention will be apparent from the drawings and detailed description, and from the claims.

DESCRIPTION OF DRAWINGS

FIG. 1 is the nucleotide sequence of a representative S1 segment (SEQ ID NO:1), S2 segment (SEQ ID NO:2), S3 segment (SEQ ID NO:3) and S4 segment (SEQ ID NO:4).

FIG. 2 is the nucleotide sequence of a representative M1 segment (SEQ ID NO:5), M2 segment (SEQ ID NO:6) and M3 segment (SEQ ID NO:7).

FIG. 3 is the nucleotide sequence of a representative L1 segment (SEQ ID NO:8), L2 segment (SEQ ID NO:9) and L3 segment (SEQ ID NO:10).

FIG. 4 is the amino acid sequence of a representative sigma-1 polypeptide (SEQ ID NO:11), sigma-2 polypeptide (SEQ ID NO:12), sigma-NS polypeptide (putative coding sequence 1, SEQ ID NO:13; putative coding sequence 2, SEQ ID NO:14) and sigma-3 polypeptide (SEQ ID NO:15).

FIG. 5 is the amino acid sequence of a representative mu-2 polypeptide (SEQ ID NO:16), mu-1 polypeptide (SEQ ID NO:17) and mu-NS polypeptide (SEQ ID NO:18).

FIG. 6 is the amino acid sequence of a representative lambda-3 polypeptide (SEQ ID NO:19), lambda-2 polypeptide (SEQ ID NO:20) and lambda-1 polypeptide (SEQ ID NO:21).

Like reference symbols in the various drawings indicate like elements.

DETAILED DESCRIPTION

This disclosure describes modifications in the nucleotide and amino acid sequence of a reovirus. Such modifications are optionally selected to affect the virus's ability to replicate and/or package itself and, therefore, alter the infectivity and/or rate of replication of a reovirus.

Reovirus Having Modified Sequences and Methods of Making

Any of the genomic segments from any type 3 mammalian orthoreovirus (referred to herein simply as "reovirus") can be

modified as disclosed herein. Representative type 3 mammalian orthoreoviruses include, without limitation, Dearing and Abney strains. See, for example, ATCC Accession Nos. VR-232 and VR-824. Reoviruses that can be modified as disclosed herein include naturally-occurring reoviruses (e.g., isolated from a source in nature such as from a patient) and reassortant reoviruses (see, e.g., U.S. Pat. No. 7,163,678).

Representative modifications to the different genomic segments of a reovirus and their manifestations in the encoded polypeptide are shown in Table 1. The modifications shown in Table 1 show modifications (both in the number of modifications and in the non-conservative nature of many of the modifications) in the sequence of segments encoding polypeptides associated with RNA-dependent RNA polymerase, transcriptional activities and/or RNA binding. For example, many of the novel modifications disclosed herein are located in the L1 genome segment. The wild-type L1 genome segment encodes a 1,267 amino acid (142 kDa) protein designated lambda-3. Lambda-3 represents the catalytic subunit of the reovirus RNA-dependent RNA polymerase, which mediates both plus- and minus-strand RNA synthesis within reovirus particles. Further modifications were observed in the M2 genome segment. The wild-type M2 genome segment encodes a 708 amino acid (76 kDa) protein designated mu-1, which is involved in the regulation of particle-bound transcription. In addition, modifications also were observed in the S4 and M1 genomic segments, which encode sigma-3 and mu-2, respectively, and play a role in transcription or single-stranded or double-stranded RNA binding.

Thus, this disclosure provides for L1, S4, M1, M2 or any combination of such genome segments that contain one or more nucleic acid modifications in the respective genome segment. Provided herein is a reovirus L1 genome segment having one or more nucleic acid modifications; a reovirus S4 genome segment having one or more nucleic acid modifications; a reovirus M1 genome segment having one or more nucleic acid modifications; and/or a M2 genome segment having one or more nucleic acid modifications.

A reovirus L1 genome segment has, for example, any combination of one or more of the following nucleotides: a T at position 660, a G at position 817, an A at position 1687, a G at position 2283, an ATG at positions 2284-2286, a C at position 2794, a C at position 2905, a C at position 2953, an A at position 3153, or a G at position 3231 (numbered relative to GenBank Accession No. M24734.1). A reovirus S4 genome segment has, for example, any combination of one or more of the following nucleotides: an A at position 74 or an A at position 624 (numbered relative to GenBank Accession No. K02739). A reovirus M1 genome segment has, for example, a T nucleotide at position 1595 (numbered relative to GenBank Accession No. AF461684.1). A reovirus M2 genome segment has, for example, a C nucleotide at position 248 (numbered relative to GenBank Accession No. M20161.1). The indicated nucleotide at the indicated position represents modifications when compared to other corresponding sequences available in public databases (e.g., GenBank Accession Nos. M24734.1, K02739, AF461684.1, and M20161.1).

A reovirus lambda-3 polypeptide has, for example, any combination of one or more amino acid residues: a Val at residue 214, an Ala at residue 267, a Thr at residue 557, a Lys at residue 755, a Met at residue 756, a Pro at residue 926, a Pro at residue 963, a Leu at residue 979, an Arg at residue 1045, or a Val at residue 1071 (numbered relative to GenBank Accession No. M24734.1). It is noted that, when the polypeptide sequence comprises a Val at residue 214 or a Val at residue 1071, the polypeptide sequence further comprises at least one

additional change in the amino acid sequence. A reovirus sigma-3 polypeptide has, for example, any combination of one or more amino acid residues: a Leu at residue 14 or a Lys at residue 198 (numbered relative to GenBank Accession No. K02739). It is noted that, when the polypeptide sequence comprises a Leu at residue 14, the polypeptide sequence further comprises at least one additional change in the amino acid sequence. A reovirus mu-1 polypeptide has, for example, an Asp at residue 73 (numbered relative to GenBank Accession No. AF461684.1). A reovirus mu-2 polypeptide has, for example, a Ser at residue 528 (numbered relative to GenBank Accession No. M20161.1). The indicated amino acid at the indicated position represents modifications when compared to other corresponding sequences in public databases (e.g., GenBank Accession Nos. M24734.1, K02739, AF461684.1, and M20161.1).

As used herein, a “non-naturally occurring” reovirus is a reovirus that has at least one nucleic acid or amino acid modification as compared to wild type sequences derived from, for example, a field isolate (e.g., a patient). “Non-naturally occurring” reovirus refers to a virus which has been manipulated or modified in the laboratory. Such manipulated or modified reoviruses include laboratory strains or mutagenized versions. These versions are distinguishable, in nucleic acid and/or amino acid sequence, from, for example, Dearing and Abney strains (e.g., ATCC VR-824 and VF-232, respectively). Representative modifications to one or more of the genome segments, the encoded polypeptide, or both are disclosed herein. In addition to a genome segment or polypeptide containing one or more of the modifications described herein, a reovirus optionally contains an S2 genome segment, which encodes the sigma-2 polypeptide. A sigma-2 polypeptide, for example, has a Cys at one or more or all of the following positions: 70, 127, 195, 241, 255, 294, 296 or 340 (numbered relative to GenBank Accession No. NP_694684.1).

A modification generally occurs at the nucleic acid level, which may or may not manifest itself in the encoded polypeptide. Modifications to a nucleic acid include, without limitation, single or multiple nucleotide transitions (purine to purine or pyrimidine to pyrimidine) or transversions (purine to pyrimidine or vice versa) and single- or multiple-nucleotide deletions or insertions. A modification in a nucleic acid can result in one or more conservative or non-conservative amino acid substitutions in the encoded polypeptide, a shift in the reading frame of translation (“frame-shift”) resulting in an entirely different polypeptide encoded from that point on, a premature stop codon resulting in a truncated polypeptide (“truncation”), or a modification in a reovirus nucleic acid may not change the encoded polypeptide at all (“silent” or “nonsense”). See, for example, Johnson & Overington, 1993, *J. Mol. Biol.*, 233:716-38; Henikoff & Henikoff, 1992, *Proc. Natl. Acad. Sci. USA*, 89:10915-19; and U.S. Pat. No. 4,554, 101 for disclosure on conservative and non-conservative amino acid substitutions.

Nucleic acids from reovirus particles are isolated, for example, using standard methodologies, which are commercially available. See also, for example, Schiff et al., “Orthoreoviruses and Their Replication,” Ch 52, in *Fields Virology*, Knipe & Howley, eds., 2006, Lippincott Williams & Wilkins. As used herein, “isolated” nucleic acids refer to nucleic acids that are substantially separated from other nucleic acids with which they are usually associated. Thus, an “isolated” nucleic acid includes, without limitation, reoviral nucleic acid that is essentially free of non-reoviral (e.g., host cell) nucleic acid, or a reoviral genomic segment that is essentially free of nucleic acid corresponding to other genomic segments. In addition,

an isolated nucleic acid includes an engineered nucleic acid such as recombinant or synthetic nucleic acids.

Modifications are generated in the nucleic acid of a reovirus using any number of methods known in the art. For example, site directed mutagenesis can be used to modify a reovirus nucleic acid sequence. One of the most common methods of site-directed mutagenesis is oligonucleotide-directed mutagenesis. In oligonucleotide-directed mutagenesis, an oligonucleotide encoding the desired change(s) in sequence is annealed to one strand of the DNA of interest and serves as a primer for initiation of DNA synthesis. In this manner, the oligonucleotide containing the sequence change is incorporated into the newly synthesized strand. See, for example, Kunkel, 1985, *Proc. Natl. Acad. Sci. USA*, 82:488; Kunkel et al., 1987, *Meth. Enzymol.*, 154:367; Lewis & Thompson, 1990, *Nucl. Acids Res.*, 18:3439; Bohnsack, 1996, *Meth. Mol. Biol.*, 57:1; Deng & Nickoloff, 1992, *Anal. Biochem.*, 200:81; and Shimada, 1996, *Meth. Mol. Biol.*, 57:157.

Other methods are routinely used in the art to introduce a modification into a sequence. For example, modified nucleic acids are generated using PCR or chemical synthesis, or polypeptides having the desired change in amino acid sequence can be chemically synthesized. See, for example, Bang & Kent, 2005, *Proc. Natl. Acad. Sci. USA*, 102:5014-9 and references therein. Selection on a cell type on which reovirus is not usually grown (e.g., human cells) and/or chemical mutagenesis (see, for example, Rudd & Lemay, 2005, *J. Gen. Virology*, 86:1489-97) also can be used to generate modifications in the nucleic acid of a reovirus. For example, the modifications shown in Table 1 were generated by culturing reovirus on human cells (e.g., human embryonic kidney (HEK) 293 cells), which are not typically used in the art of culturing reovirus. In contrast, cells that are commonly used to culture reovirus are described in, for example, Tyler, "Mammalian Reoviruses," Ch 53, page 1731-2, in *Fields Virology*, Knipe & Howley, eds., 2006, Lippincott Williams & Wilkins. The modifications described herein represent an adaptation by the reovirus to human cells. There was also a selection step at each of these plaque purification steps by selection the largest plaque (triple plaque purification), thus a growth or virulence advantage in these cells.

After one or more modifications have been introduced into a reovirus nucleic acid or polypeptide, virus particles are reconstituted using methods known in the art. See, for example, Schiff et al., "Orthoreoviruses and Their Replication," Ch 52, in *Fields Virology*, Knipe & Howley, eds., 2006, Lippincott Williams & Wilkins; Smith et al., 1969, *Virology*, 39(4):791-810; and U.S. Pat. Nos. 7,186,542; 7,049,127; 6,808,916; and 6,528,305. Reoviruses having one or more modifications in their sequence are cultured in, for example, mouse L929 cells or neoplastic cells (e.g., MCF7 (ATCC Accession No. HTB-22), SKBR3 (ATCC Accession No. HTB-30), or MDA MB 468 (ATCC Accession No. HTB 132) cells), and selected based on any number of characteristics that may indicate, for example, a growth advantage over a reovirus that does not contain one or more modifications. Reoviruses are selected following culturing in a cell line (neoplastic or otherwise) and/or following infection of an animal model system.

Such characteristics include, without limitation, an increased rate of lysis; an increased size of plaque formation; an increased rate of RNA replication; an increased rate of RNA transcription; an increased rate of translation; an increased rate of virus assembly and/or packaging; an increased number of viral progeny; an increased ability of a reovirus to be taken up by a host cell; an increased or

enhanced ability to uncoat; enhanced cell lysis or inducement to cell death including apoptosis, necrosis or autophagy; an enhanced ability to infect, lyse and kill human neoplastic cells lines; decreased immunogenicity in mammalian cells; differential susceptibility to interferon sensitivity; decreased toxicity toward the host; enhanced drug interaction; enhanced radiotherapy interaction; or the ability to release effective tumor epitopes. Additionally, reoviruses having a modified sequence are selected, for example, for the ability to lytically infect a mammalian cell having an active Ras pathway. See, for example, U.S. Pat. No. 7,052,832.

Reovirus particles are obtained using any number of methods known in the art. For example, reoviruses are cultured in L929 mouse fibroblast cells or human cells (e.g., HEK 293), and the viral particles purified using standard methodology. See, for example, Schiff et al., "Orthoreoviruses and Their Replication," Ch 52, in *Fields Virology*, Knipe & Howley, eds., 2006, Lippincott Williams & Wilkins; Smith et al., 1969, *Virology*, 39(4):791-810; and U.S. Pat. Nos. 7,186,542; 7,049,127; 6,808,916; and 6,528,305. As used herein, "purified" viral particles refers to virus particles that have been substantially separated from cellular components that naturally accompany it. Typically, virus particles are considered "purified" when they are at least 70% (e.g., at least 75%, 80%, 85%, 90%, 95%, or 99%) by dry weight, free from the proteins and other cellular components with which the viruses are naturally associated.

A reovirus having the nucleic acid sequence shown in FIGS. 1, 2 and 3 (SEQ ID NOs: 1-10) and the amino acid sequence shown in FIGS. 4, 5, and 6 (SEQ ID NOs: 11-20), which contain the nucleotide and amino acid modifications shown in Table 1, was deposited with the International Depositary Authority of Canada (IDAC, National Microbiology Laboratory, Public Health Agency of Canada, 1015 Arlington St., Winnipeg, Manitoba Canada R3E 3R2) on Sep. 19, 2007, and assigned Accession No. 190907-01. This deposit will be maintained under the terms of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure. This deposit is exemplary and was made merely as a convenience for those of skill in the art and is not an admission that a deposit is required for patentability (e.g., under 35 U.S.C. §112).

Methods of Using Reoviruses Having Modified Sequences

As described previously (see, for example, U.S. Pat. Nos. 6,110,461; 6,136,307; 6,261,555; 6,344,195; 6,576,234; and 6,811,775), reoviruses use a host cell's Ras pathway machinery to downregulate double-stranded RNA-activated protein kinase (PKR) and thus replicate in the cell. Based upon these discoveries, methods have been developed for using reovirus to treat proliferative disorders in mammals. Representative mammals include mice, dogs, cats, sheep, goats, cows, horses, pigs, non-human primates, and humans. As used herein, a "patient" includes any mammal with a proliferative disorder.

A "proliferative disorder" is any cellular disorder in which the cells proliferate more rapidly than normal tissue growth. Thus a "proliferating cell" is a cell that is proliferating more rapidly than normal cells. A proliferative disorder includes, but is not limited to, neoplasms, which are also referred to as tumors. A neoplasm includes, but is not limited to, pancreatic cancer, breast cancer, brain cancer (e.g., glioblastoma), lung cancer, prostate cancer, colorectal cancer, thyroid cancer, renal cancer, adrenal cancer, liver cancer, neurofibromatosis, and leukemia. A neoplasm includes a solid neoplasm (e.g. sarcoma or carcinoma) or a cancerous growth affecting the

hematopoietic system (e.g., lymphoma or leukemia). Other proliferative disorders include, but are not limited to neurofibromatosis.

Generally, in proliferative disorders for which reovirus is used as a treatment, at least some of the proliferating cells have a mutation in which the Ras gene (or an element of the Ras signaling pathway) is activated, either directly (e.g., by an activating mutation in Ras) or indirectly (e.g., by activation of an upstream or downstream element in the Ras pathway). Activation of an upstream element in the Ras pathway includes, for example, transformation with epidermal growth factor receptor (EGFR) or Sos. See, for example, Wiessmuller & Wittinghofer, 1994, *Cellular Signaling*, 6(3): 247-267; and Barbacid, 1987, *Ann. Rev. Biochem.*, 56, 779-827. Activation of a downstream element in the Ras pathway includes, for example, a mutation within B-Raf. See, for example, Brose et al., 2002, *Cancer Res.*, 62:6997-7000. In addition, reovirus is useful for treating proliferative disorders caused by mutations or dysregulation of PKR. See, for example, Strong et al., 1998, *EMBO J.*, 17:3351-662.

A reovirus having a modified sequence as disclosed herein is administered to a mammal that has a proliferative disorder. As used herein, administration refers to delivery of a reovirus such that the reovirus contacts the proliferating cells. The route by which a reovirus is administered depends on the type of disorder and the location of the proliferating cells. A wide variety of administration routes can be employed. For example, for a solid neoplasm that is accessible, a reovirus is administered by direct injection. For a hematopoietic neoplasm, for example, a reovirus is administered intravenously or intravascularly. For certain neoplasms, e.g., those not easily accessible within the body such as metastases or brain tumors, a reovirus is administered in a manner such that it is transported systemically through the body of the mammal to thereby reach the neoplasm (e.g., intrathecally, intravenously, intramuscularly, subcutaneously, or intra-peritoneally). A reovirus also is administered locally including, for example, topically (e.g., for melanoma), orally (e.g., for oral or esophageal neoplasm), rectally (e.g., for colorectal neoplasm), vaginally (e.g., for cervical or vaginal neoplasm), nasally or by inhalation (e.g., for lung neoplasm). A reovirus is optionally administered by more than one route and/or to more than one location in an individual.

Targeted administration may be used to administer a reovirus. For example, dendritic cells containing a reovirus may be administered to a subject. See, for example, US Publication No. 2008/0014183. In another example of targeted delivery, carrier cells may be used to target cells of a proliferative disorder and prevent immune recognition of a reovirus which they carry. See, for example, Qiao et al., 2008, *Nature Med.*, 14:37-44; and WO 2008/009115.

A reovirus having a modified sequence as disclosed herein is administered in an amount that is sufficient to treat the proliferative disorder (e.g., an "effective amount"). A proliferative disorder is "treated" when administration of a reovirus having a modified sequence to proliferating cells affects one or more symptoms or clinical signs of the disorder including, e.g., increasing lysis (e.g., "oncolysis") of the cells, reducing the number of proliferating cells, reducing the size or progression of a neoplasm, reducing pain associated with the neoplasm, as compared to the signs or symptoms in the absence of the treatment. As used herein, the term "oncolysis" means at least 10% of the proliferating cells are lysed (e.g., at least 20%, 30%, 40%, 50%, or 75% of the cells are lysed). The percentage of lysis can be determined, for example, by measuring the reduction in the size of a neoplasm or in the number

of proliferating cells in a mammal, or by measuring the amount of lysis of cells in vitro (e.g., from a biopsy of the proliferating cells).

An effective amount of a reovirus having a modified sequence is determined on an individual basis and is based, at least in part, on the particular reovirus used; the individual's size, age, gender; and the size and other characteristics of the proliferating cells. For example, for treatment of a human, approximately 10^3 to 10^{12} plaque forming units (PFU) of a reovirus is used, depending on the type, size and number of proliferating cells or neoplasms present. The effective amount can be from about 1.0 PFU/kg body weight to about 10^{15} PFU/kg body weight (e.g., from about 10^2 PFU/kg body weight to about 10^{13} PFU/kg body weight). A reovirus is administered in a single dose or in multiple doses (e.g., two, three, four, six, or more doses). Multiple doses are administered concurrently or consecutively (e.g., over a period of days or weeks). Treatment with a reovirus having a modified sequence lasts from several days to several months or until diminution of the disease is achieved.

It is contemplated that a reovirus having a modified sequence as disclosed herein is optionally administered in conjunction with surgery or removal of proliferating cells (e.g., a neoplasm). It also is contemplated that a reovirus having a modified sequence is optionally administered in conjunction with or in addition to radiation therapy. It is further contemplated that a reovirus having a modified sequence is optionally administered in conjunction with or in addition to known anticancer compounds, chemotherapeutic agents, and/or immunosuppressive agents. Such agents, include, but are not limited to, 5-fluorouracil, mitomycin C, methotrexate, hydroxyurea, gemcitabine, cyclophosphamide, dacarbazine, mitoxantrone, anthracyclins (Epirubicin, Irinotecan, and Doxorubicin), antibodies to receptors such as herceptin, topoisomerase inhibitors such as etoposide or camptothecin, pregnasome, platinum compounds such as carboplatin and cisplatin, taxanes such as taxol and taxotere, hormone therapies such as tamoxifen and anti-estrogens, interleukins, interferons, aromatase inhibitors, progestational agents, LHRH analogs, mTOR inhibitors (e.g., rapamycin and derivatives thereof; see, for example, Homicsko et al., 2005, *Cancer Res.*, 65:6882-90; and Rao et al., 2004, *Curr. Cancer Drug Targets*, 4:621-35), and combinations thereof.

It is further contemplated that a reovirus having a modified sequence is administered in conjunction with an agent that can increase endothelial permeability and/or decrease interstitial fluid pressure. Such agents include, for example, TNF- α . See, for example, Sacchi et al., 2006, *Clin. Cancer Res.*, 12:175-182. It is contemplated that a reovirus having a modified sequence can be administered in conjunction with any combination of the therapies and agents described herein.

Pharmaceutical Compositions

Pharmaceutical compositions that include one or more reoviruses, at least one of which has a modified sequence as described herein, are provided. See, for example, U.S. Pat. No. 6,576,234. In addition to one or more reoviruses, at least one of which has a modified sequence, a pharmaceutical composition typically includes a pharmaceutically acceptable carrier. A pharmaceutically acceptable carrier includes a solid, semi-solid, or liquid material that acts as a vehicle, carrier or medium for the reovirus. Thus, for example, compositions containing a reovirus having a modified sequence are in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active

compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

Some examples of suitable carriers include phosphate-buffered saline or another physiologically acceptable buffer, lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, sterile water, syrup, and methyl cellulose. A pharmaceutical composition additionally can include, without limitation, lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. Pharmaceutical compositions of the invention can be formulated to provide quick, sustained or delayed release of a reovirus having a modified sequence after administration by employing procedures known in the art. In addition to the representative formulations described below, other suitable formulations for use in a pharmaceutical composition are found in *Remington: The Science and Practice of Pharmacy* (2003, Gennaro & Gennaro, eds., Lippincott Williams & Wilkens).

For preparing solid compositions such as tablets, a reovirus having a modified sequence is mixed with a pharmaceutical carrier to form a solid composition. Optionally, tablets or pills are coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, a tablet or pill comprises an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components, for example, are separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials are used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

Liquid formulations that include a reovirus having a modified sequence for oral administration or for injection generally include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as corn oil, cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. These liquid or solid compositions optionally contain suitable pharmaceutically acceptable excipients as described herein. Such compositions are administered, for example, by the oral or nasal respiratory route for local or systemic effect. Compositions in pharmaceutically acceptable solvents are nebulized by use of inert gases. Nebulized solutions are inhaled, for example, directly from the nebulizing device, from an attached face mask tent, or from an intermittent positive pressure breathing machine. Solution, suspension, or powder compositions are administered, orally or nasally, for example, from devices which deliver the formulation in an appropriate manner.

Another formulation that is employed in the methods taught herein employs transdermal delivery devices ("patches"). Such transdermal patches are used to provide continuous or discontinuous infusion of a reovirus having a modified sequence. The construction and use of transdermal patches for the delivery of pharmaceutical agents are performed according to methods known in the art. See, for example, U.S. Pat. No. 5,023,252. Such patches are con-

structed for continuous, pulsatile, or on-demand delivery of a reovirus having a modified sequence.

A reovirus having a modified sequence is optionally chemically or biochemically pretreated (e.g., by treatment with a protease such as chymotrypsin or trypsin) prior to administration (e.g., prior to inclusion in the pharmaceutical composition). Pretreatment with a protease removes the outer coat or capsid of the virus and can be used to increase the infectivity of the virus. Additionally or alternatively, a reovirus having a modified sequence is coated in a liposome or micelle to reduce or prevent an immune response in a mammal that has developed immunity toward a reovirus. Such reoviruses are referred to as "immunoprotected reoviruses." See, for example, U.S. Pat. Nos. 6,565,831 and 7,014,847.

A reovirus having a modified sequence or a pharmaceutical composition comprising such a reovirus can be packaged into a kit. It is contemplated that a kit optionally includes one or more chemotherapeutic agents and/or immunosuppressive agents (e.g., anti-antireovirus antibodies). A pharmaceutical composition, for example, is formulated in a unit dosage form. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of a reovirus having a modified sequence calculated to produce the desired therapeutic effect in association with a suitable pharmaceutically acceptable carrier.

In accordance with the present invention, there may be employed conventional molecular biology, microbiology, biochemical, and recombinant DNA techniques within the skill of the art. Such techniques are explained fully in the literature. The invention will be further described in the following examples, which do not limit the scope of the invention described in the claims.

EXAMPLES

Example 1

Sequencing and Analysis

Cultures for production of reovirus were initiated from a suspension-adapted HEK 293 S Master Cell Bank (MCB). HEK 293 cells were maintained in Serum Free Medium (HEK 293 SFM II) supplemented with L-glutamine. HEK 293 cells were expanded and seeded into three 15 L spinner flasks, and further expanded until there was 12 L in each of the three flasks. Infection of the HEK 293 cells by reovirus was performed by direct inoculation of the virus into the cell culture. The virus was harvested when the viability of the HEK 293 S cells had decreased by 20-50% post-infection. The virus material from all three spinners was pooled in a single sterile container and agitated to create a homogeneous mixture. Three liters of the pooled cell suspension was removed, transferred to conical tubes, and centrifuged at ~3000 rpm for 15 minutes. The cells were then resuspended with 100 mL of clarified conditioned medium, snap frozen in an alcohol-dry ice bath three times, and then filled into sterile, labeled cryovials for use as a seed stock.

A viral stock was prepared by performing a three-time plaque purification. Adherent HEK 293 S cells were plated onto 6-well tissue culture plates, infected with the seed stock described above, and two of the largest plaques were picked. These two plaques were separately amplified and harvested and two of the largest plaques were picked again. This procedure was repeated again for a total of three times. Of the two plaques, one was selected as seed stock for subsequent expansions.

Cultures were initiated from the same suspension adapted HEK 293 S MCB described above and were maintained in the same HEK 293 Serum Free Medium (HEK 293 SFM II) supplemented with L-glutamine. Cells were expanded from T-flasks up to multiple 3 L spinner flasks. The infection was performed by first diluting the plaque-purified virus in HEK 293 SFM media and then adding 8 to 12 mL of the diluted virus into the cell culture. The virus was harvested when the viability of the HEK 293 S cells had decreased by 20-50% following infection, and microscopic examination of each of the spinners confirmed the lack of microbial contamination and that a cytopathic effect (CPE) was present in the cells.

alcohol-dry ice bath three times to lyse the cells and then filled into sterile, labeled cryovials for use in sequencing reactions. Both RNA strands were sequenced from both directions, and the sequence of each of the 10 genomic segments was assembled from the overlapping contigs. The assembled sequence of each genomic segment was used in a BLAST search of the NCBI database on the World Wide Web. Alignments with three or four different reovirus sequences found in the NCBI database were examined and the alignment having the highest amount of homology was used for further analysis. The polymorphisms or modifications compared to other reported sequences are shown in Table 1. Those modifications that are unique to the selected reovirus strain are indicated with an asterisk in Table 1.

TABLE 1

Modifications Identified			
Genomic Segment	Position (nucleotide; amino acid)	Published Sequence (nucleotide; amino acid)	Novel Polymorphism (nucleotide; amino acid)
S1		GenBank Accession No. M10262.1	SEQ ID NO: 1
	499; 163	A; Thr	T; Ser
S3		GenBank Accession No. X01627.1	SEQ ID NO: 3
	1057; 344	T; <i>Leu</i>	C; <i>Leu</i>
S4		GenBank Accession No. K02739	SEQ ID NO: 4
*	74; 14	G; <i>Leu</i>	A; <i>Leu</i>
*	624; 198	G; Glu	A; Lys
	719; 229	G; Glu	T; Asp
M1		GenBank Accession No. AF461684.1	SEQ ID NO: 5
	1129; 372	G; Met	T; Ile
*	1595; 528	G; Ala	T; Ser
M2		GenBank Accession No. M20161.1	SEQ ID NO: 6
*	248; 73	A; Glu	C; Asp
	302; 91	G; <i>Ala</i>	C; <i>Ala</i>
	303; 92	C; <i>Leu</i>	T; <i>Leu</i>
	305; 92	T; <i>Leu</i>	G; <i>Leu</i>
	709-10; 227	CG; Thr	GC; Ser
	1173; 382	T; <i>Leu</i>	C; <i>Leu</i>
L1		GenBank Accession No. M24734.1	SEQ ID NO: 8
*	660; 214	A; <i>Val</i>	T; <i>Val</i>
*	817; 267	T; Ser	G; Ala
*	1687; 557	C; Pro	A; Thr
*	2283; 755	C; Asn	G; Lys
*	2284-6; 756	GAT; Asp	ATG; Met
*	2794; 926	A; Thr	C; Pro
*	2905; 963	T; Ser	C; Pro
*	2953; 979	A; Met	C; Leu
*	3153; 1045	C; Ser	A; Arg
*	3231; 1071	T; <i>Val</i>	G; <i>Val</i>
L2		GenBank Accession No. J03488.1	SEQ ID NO: 9
	1838-40; 609	TTT; Phe	GGG; Gly
	3703; 1230	A; <i>Leu</i>	G; <i>Leu</i>
L3		GenBank Accession No. AF129822	SEQ ID NO: 10
	1512; 500	T; Ile	G; Ser
	2569; 852	G; Gln	T; His

* designates unique modifications; italicized residues indicate silent modifications; position numbers are with respect to the indicated GenBank Accession No.

CPE was indicated by cells having a swollen and granular appearance. The material from the spinners was pooled in a single sterile container, agitated to create a homogeneous mixture, and a bulk harvest sample removed. The remaining pooled cell suspension was transferred to conical tubes and centrifuged at ~3000 rpm for 15 minutes. The cells were then resuspended with 400 mL of clarified conditioned medium, and the concentrated cell suspension was snap-frozen in an

It is to be understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims. Disclosed are materials, compositions, and components that can be used for, can be used in conjunction with, can be

used in preparation for, or are products of the disclosed method and compositions. These and other materials are disclosed herein, and it is understood that when combinations, subsets, interactions, groups, etc. of these materials are disclosed that while specific reference of each various individual and collective combinations and permutation of these compounds may not be explicitly disclosed, each is specifically contemplated and described herein. For example, if a particu-

lar modification of a reovirus or treatment regime is disclosed and discussed and a number of modifications that can be made to the reovirus or regime are discussed, each and every combination and permutation of the reovirus and the regime are specifically contemplated unless specifically indicated to the contrary. Likewise, any subset or combination of these is also specifically contemplated and disclosed.

SEQUENCE LISTING

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Cys	Met	Asp	Met	Asp	Val	Arg	Trp	Thr	Arg	Ile	Ala	Gly	Arg	Leu	Val
	210					215					220				
Ile	Arg	Val	Trp	Thr	Leu	His	Ala	Ala	Ser	Thr	Ser	Cys	Ile	Ala	Arg
225					230				235						240
Arg	Gln	Gln	Lys	Pro	Ser	Val	Cys	Leu	Arg	His	Ala	Leu	Cys		
			245						250						
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			20					25					30		
Thr	Thr	Lys	Val	Val	Arg	Asn	Val	Val	Glu	Tyr	Gln	Ile	Arg	Thr	Gly
		35					40					45			
Gly	Phe	Phe	Ser	Cys	Leu	Ala	Met	Leu	Arg	Pro	Leu	Gln	Tyr	Ala	Lys
	50					55				60					
Arg	Glu	Arg	Leu	Leu	Gly	Gln	Arg	Asn	Leu	Glu	Arg	Ile	Ser	Thr	Arg
65					70					75					80
Asp	Ile	Leu	Gln	Thr	Arg	Asp	Leu	His	Ser	Leu	Cys	Met	Pro	Thr	Pro
				85					90					95	
Asp	Ala	Pro	Met	Ser	Asn	His	Gln	Ala	Ser	Thr	Met	Arg	Glu	Leu	Ile
			100					105						110	
Cys	Ser	Tyr	Phe	Lys	Val	Asp	His	Ala	Asp	Gly	Leu	Lys	Tyr	Ile	Pro
		115					120					125			
Met	Asp	Glu	Arg	Tyr	Ser	Pro	Ser	Ser	Leu	Ala	Arg	Leu	Phe	Thr	Met
	130					135					140				
Gly	Met	Ala	Gly	Leu	His	Ile	Thr	Thr	Glu	Pro	Ser	Tyr	Lys	Arg	Val
145					150					155					160
Pro	Ile	Met	His	Leu	Ala	Ala	Asp	Leu	Asp	Cys	Met	Thr	Leu	Ala	Leu
			165						170					175	
Pro	Tyr	Met	Ile	Thr	Leu	Asp	Gly	Asp	Thr	Val	Val	Pro	Val	Ala	Pro
		180						185					190		
Thr	Leu	Ser	Ala	Glu	Gln	Leu	Leu	Asp	Asp	Gly	Leu	Lys	Gly	Leu	Ala
		195					200					205			
Cys	Met	Asp	Ile	Ser	Tyr	Gly	Cys	Glu	Val	Asp	Ala	Asn	Ser	Arg	Pro
	210					215					220				
Ala	Gly	Asp	Gln	Ser	Met	Asp	Ser	Ser	Arg	Cys	Ile	Asn	Glu	Leu	Tyr
225					230					235					240
Cys	Glu	Glu	Thr	Ala	Glu	Ala	Ile	Cys	Val	Leu	Lys	Thr	Cys	Leu	Val
				245					250					255	
Leu	Asn	Cys	Met	Gln	Phe	Lys	Leu	Glu	Met	Asp	Asp	Leu	Ala	His	Asn
			260					265					270		
Ala	Ala	Glu	Leu	Asp	Lys	Ile	Gln	Met	Met	Ile	Pro	Phe	Ser	Glu	Arg
		275					280					285			
Val	Phe	Arg	Met	Ala	Ser	Ser	Phe	Ala	Thr	Ile	Asp	Ala	Gln	Cys	Phe
	290					295					300				
Arg	Phe	Cys	Val	Met	Met	Lys	Asp	Lys	Asn	Leu	Lys	Ile	Asp	Met	Arg
305					310					315					320
Glu	Thr	Thr	Arg	Leu	Trp	Thr	Arg	Ser	Ala	Ser	Asp	Asp	Ser	Val	Ala
				325					330					335	

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Thr	Ser	Ser	Leu	Ser	Ile	Ser	Leu	Asp	Arg	Gly	Arg	Trp	Val	Ala	Ala	
			340					345					350			
Asp	Ala	Ser	Asp	Ala	Arg	Leu	Leu	Val	Phe	Pro	Ile	Arg	Val			
		355					360					365				
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1				5					10					15		
Asn	Ala	Phe	Glu	Gly	Arg	Val	Ser	Ile	Tyr	Ser	Ala	Gln	Glu	Gly	Trp	
			20					25					30			
Asp	Lys	Thr	Ile	Ser	Ala	Gln	Pro	Asp	Met	Met	Val	Cys	Gly	Gly	Ala	
		35					40					45				
Val	Val	Cys	Met	His	Cys	Leu	Gly	Val	Val	Gly	Ser	Leu	Gln	Arg	Lys	
	50					55				60						
Leu	Lys	His	Leu	Pro	His	His	Arg	Cys	Asn	Gln	Gln	Ile	Arg	His	Gln	
65					70					75					80	
Asp	Tyr	Val	Asp	Val	Gln	Phe	Ala	Asp	Arg	Val	Thr	Ala	His	Trp	Lys	
				85					90					95		
Arg	Gly	Met	Leu	Ser	Phe	Val	Ala	Gln	Met	His	Glu	Met	Met	Asn	Asp	
			100					105					110			
Val	Ser	Pro	Asp	Asp	Leu	Asp	Arg	Val	Arg	Thr	Glu	Gly	Gly	Ser	Leu	
		115					120					125				
Val	Glu	Leu	Asn	Arg	Leu	Gln	Val	Asp	Pro	Asn	Ser	Met	Phe	Arg	Ser	
	130					135					140					
Ile	His	Ser	Ser	Trp	Thr	Asp	Pro	Leu	Gln	Val	Val	Asp	Asp	Leu	Asp	
145					150					155					160	
Thr	Lys	Leu	Asp	Gln	Tyr	Trp	Thr	Ala	Leu	Asn	Leu	Met	Ile	Asp	Ser	
			165						170					175		
Ser	Asp	Leu	Ile	Pro	Asn	Phe	Met	Met	Arg	Asp	Pro	Ser	His	Ala	Phe	
		180						185					190			
Asn	Gly	Val	Lys	Leu	Lys	Gly	Asp	Ala	Arg	Gln	Thr	Gln	Phe	Ser	Arg	
		195					200					205				
Thr	Phe	Asp	Ser	Arg	Ser	Ser	Leu	Glu	Trp	Gly	Val	Met	Val	Tyr	Asp	
	210					215					220					
Tyr	Ser	Glu	Leu	Asp	His	Asp	Pro	Ser	Lys	Gly	Arg	Ala	Tyr	Arg	Lys	
225					230					235					240	
Glu	Leu	Val	Thr	Pro	Ala	Arg	Asp	Phe	Gly	His	Phe	Gly	Leu	Ser	His	
			245						250					255		
Tyr	Ser	Arg	Ala	Thr	Thr	Pro	Ile	Leu	Gly	Lys	Met	Pro	Ala	Val	Phe	
		260					265						270			
Ser	Gly	Met	Leu	Thr	Gly	Asn	Cys	Lys	Met	Tyr	Pro	Phe	Ile	Lys	Gly	
		275					280					285				
Thr	Ala	Lys	Leu	Lys	Thr	Val	Arg	Lys	Leu	Val	Glu	Ala	Val	Asn	His	
	290					295					300					
Ala	Trp	Gly	Val	Glu	Lys	Ile	Arg	Tyr	Ala	Leu	Gly	Pro	Gly	Gly	Met	
305				310						315					320	
Thr	Gly	Trp	Tyr	Asn	Arg	Thr	Met	Gln	Gln	Ala	Pro	Ile	Val	Leu	Thr	
			325						330					335		
Pro	Ala	Ala	Leu	Thr	Met	Phe	Pro	Asp	Thr	Ile	Lys	Phe	Gly	Asp	Leu	
		340						345						350		

Met 1	Ala	Tyr	Ile	Ala 5	Val	Pro	Ala	Val	Val 10	Asp	Ser	Arg	Ser	Ser 15	Glu
Ala	Ile	Gly	Leu 20	Leu	Glu	Ser	Phe	Gly 25	Val	Asp	Ala	Gly	Ala 30	Asp	Ala
Asn	Asp	Val 35	Ser	Tyr	Gln	Asp	His 40	Asp	Tyr	Val	Leu	Asp 45	Gln	Leu	Gln
Tyr	Met 50	Leu	Asp	Gly	Tyr	Glu 55	Ala	Gly	Asp	Val	Ile 60	Asp	Ala	Leu	Val
His 65	Lys	Asn	Trp	Leu	His 70	His	Ser	Val	Tyr	Cys 75	Leu	Leu	Pro	Pro	Lys 80
Ser	Gln	Leu	Leu	Glu 85	Tyr	Trp	Lys	Ser	Asn 90	Pro	Ser	Ala	Ile	Pro 95	Asp
Asn	Val	Asp	Arg 100	Arg	Leu	Arg	Lys	Arg 105	Leu	Met	Leu	Lys	Lys 110	Asp	Leu
Arg	Lys	Asp 115	Asp	Glu	Tyr	Asn	Gln 120	Leu	Ala	Arg	Ala	Phe 125	Lys	Ile	Ser
Asp 130	Val	Tyr	Ala	Pro	Leu	Ile 135	Ser	Ser	Thr	Thr	Ser 140	Pro	Met	Thr	Met
Ile 145	Gln	Asn	Leu	Asn 150	Arg	Gly	Glu	Ile	Val	Tyr 155	Thr	Thr	Thr	Asp	Arg 160
Val	Ile	Gly	Ala	Arg 165	Ile	Leu	Leu	Tyr	Ala 170	Pro	Arg	Lys	Tyr	Tyr 175	Ala
Ser	Thr	Leu	Ser 180	Phe	Thr	Met	Thr	Lys 185	Cys	Ile	Ile	Pro	Phe 190	Gly	Lys
Glu	Val	Gly 195	Arg	Val	Pro	His	Ser 200	Arg	Phe	Asn	Val	Gly 205	Thr	Phe	Pro
Ser 210	Ile	Ala	Thr	Pro	Lys	Cys 215	Phe	Val	Met	Ser	Gly 220	Val	Asp	Ile	Glu
Ser 225	Ile	Pro	Asn	Glu	Phe 230	Ile	Lys	Leu	Phe	Tyr 235	Gln	Arg	Val	Lys	Ser 240
Val	His	Ala	Asn 245	Ile	Leu	Asn	Asp	Ile	Ser 250	Pro	Gln	Ile	Val	Ser 255	Asp
Met	Ile	Asn	Arg 260	Lys	Arg	Leu	Arg	Val 265	His	Thr	Pro	Ser	Asp 270	Arg	Arg
Ala	Ala	Gln 275	Leu	Met	His	Leu	Pro 280	Tyr	His	Val	Lys	Arg 285	Gly	Ala	Ser
His 290	Val	Asp	Val	Tyr	Lys 295	Val	Asp	Val	Val	Asp	Met 300	Leu	Phe	Glu	Val
Val 305	Asp	Val	Ala	Asp	Gly 310	Leu	Arg	Asn	Val	Ser 315	Arg	Lys	Leu	Thr	Met 320
His	Thr	Val	Pro	Val 325	Cys	Ile	Leu	Glu	Met 330	Leu	Gly	Ile	Glu	Ile 335	Ala
Asp	Tyr	Cys	Ile 340	Arg	Gln	Glu	Asp	Gly 345	Met	Leu	Thr	Asp	Trp 350	Phe	Leu
Leu	Leu	Thr 355	Met	Leu	Ser	Asp	Gly 360	Leu	Thr	Asp	Arg	Arg 365	Thr	His	Cys

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Gln	Tyr	Leu	Ile	Asn	Pro	Ser	Ser	Val	Pro	Pro	Asp	Val	Ile	Leu	Asn
370						375					380				
Ile	Ser	Ile	Thr	Gly	Phe	Ile	Asn	Arg	His	Thr	Ile	Asp	Val	Met	Pro
385					390					395					400
Asp	Ile	Tyr	Asp	Phe	Val	Lys	Pro	Ile	Gly	Ala	Val	Leu	Pro	Lys	Gly
				405					410					415	
Ser	Phe	Lys	Ser	Thr	Ile	Met	Arg	Val	Leu	Asp	Ser	Ile	Ser	Ile	Leu
			420					425					430		
Gly	Ile	Gln	Ile	Met	Pro	Arg	Ala	His	Val	Val	Asp	Ser	Asp	Glu	Val
		435					440					445			
Gly	Glu	Gln	Met	Glu	Pro	Thr	Phe	Glu	Gln	Ala	Val	Met	Glu	Ile	Tyr
	450					455					460				
Lys	Gly	Ile	Ala	Gly	Val	Asp	Ser	Leu	Asp	Asp	Leu	Ile	Lys	Trp	Val
465					470					475					480
Leu	Asn	Ser	Asp	Leu	Ile	Pro	His	Asp	Asp	Arg	Leu	Gly	Gln	Leu	Phe
				485					490					495	
Gln	Ala	Phe	Leu	Pro	Leu	Ala	Lys	Asp	Leu	Leu	Ala	Pro	Met	Ala	Arg
			500					505					510		
Lys	Phe	Tyr	Asp	Asn	Ser	Met	Ser	Glu	Gly	Arg	Leu	Leu	Thr	Phe	Ser
		515					520						525		
His	Ala	Asp	Ser	Glu	Leu	Leu	Asn	Ala	Asn	Tyr	Phe	Gly	His	Leu	Leu
	530						535				540				
Arg	Leu	Lys	Ile	Pro	Tyr	Ile	Thr	Glu	Val	Asn	Leu	Met	Ile	Arg	Lys
545					550					555					560
Asn	Arg	Glu	Gly	Gly	Glu	Leu	Phe	Gln	Leu	Val	Leu	Ser	Tyr	Leu	Tyr
				565					570					575	
Lys	Met	Tyr	Ala	Thr	Ser	Ala	Gln	Pro	Lys	Trp	Phe	Gly	Ser	Leu	Leu
			580					585					590		
Arg	Leu	Leu	Ile	Cys	Pro	Trp	Leu	His	Met	Glu	Lys	Leu	Ile	Gly	Glu
		595					600					605			
Ala	Asp	Pro	Ala	Ser	Thr	Ser	Ala	Glu	Ile	Gly	Trp	His	Ile	Pro	Arg
	610					615					620				
Glu	Gln	Leu	Met	Gln	Asp	Gly	Trp	Cys	Gly	Cys	Glu	Asp	Gly	Phe	Ile
625					630					635					640
Pro	Tyr	Val	Ser	Ile	Arg	Ala	Pro	Arg	Leu	Val	Ile	Glu	Glu	Leu	Met
				645					650					655	
Glu	Lys	Asn	Trp	Gly	Gln	Tyr	His	Ala	Gln	Val	Ile	Val	Thr	Asp	Gln
			660					665					670		
Leu	Val	Val	Gly	Glu	Pro	Arg	Arg	Val	Ser	Ala	Lys	Ala	Val	Ile	Lys
		675					680					685			
Gly	Asn	His	Leu	Pro	Val	Lys	Leu	Val	Ser	Arg	Phe	Ala	Cys	Phe	Thr
	690					695					700				
Leu	Thr	Ala	Lys	Tyr	Glu	Met	Arg	Leu	Ser	Cys	Gly	His	Ser	Thr	Gly
705					710					715					720
Arg	Gly	Ala	Ala	Tyr	Ser	Ala	Arg	Leu	Ala	Phe	Arg	Ser	Asp	Leu	Ala
				725					730					735	
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Gly	Asn	Val	Phe	Lys	Pro	Ser	Ala	Glu	Thr	Ser	Ser	Thr	Ala	Val	Pro	
			20					25					30			
Ser	Leu	Ser	Leu	Ser	Pro	Gly	Met	Leu	Asn	Pro	Gly	Gly	Val	Pro	Trp	
	35						40					45				
Ile	Ala	Val	Gly	Asp	Glu	Thr	Ser	Val	Thr	Ser	Pro	Gly	Ala	Leu	Arg	
	50					55					60					
Arg	Met	Thr	Ser	Lys	Asp	Ile	Pro	Asp	Thr	Ala	Ile	Ile	Asn	Thr	Asp	
65					70					75					80	
Asn	Ser	Ser	Gly	Ala	Val	Pro	Ser	Glu	Ser	Ala	Leu	Val	Pro	Tyr	Ile	
				85					90					95		
Asp	Glu	Pro	Leu	Val	Val	Val	Thr	Glu	His	Ala	Ile	Thr	Asn	Phe	Thr	
			100					105					110			
Lys	Ala	Glu	Met	Ala	Leu	Glu	Phe	Asn	Arg	Glu	Phe	Leu	Asp	Lys	Met	
		115					120					125				
Arg	Val	Leu	Ser	Val	Ser	Pro	Lys	Tyr	Ser	Asp	Leu	Leu	Thr	Tyr	Val	
	130					135					140					
Asp	Cys	Tyr	Val	Gly	Val	Ser	Ala	Arg	Gln	Ala	Leu	Asn	Asn	Phe	Gln	
145					150					155					160	
Lys	Gln	Val	Pro	Val	Ile	Thr	Pro	Thr	Arg	Gln	Thr	Met	Tyr	Val	Asp	
				165					170					175		
Ser	Ile	Gln	Ala	Ala	Leu	Lys	Ala	Leu	Glu	Lys	Trp	Glu	Ile	Asp	Leu	
			180					185					190			
Arg	Val	Ala	Gln	Thr	Leu	Leu	Pro	Thr	Asn	Val	Pro	Ile	Gly	Glu	Val	
		195					200					205				
Ser	Cys	Pro	Met	Gln	Ser	Val	Val	Lys	Leu	Leu	Asp	Asp	Gln	Leu	Pro	
	210					215					220					
Asp	Asp	Ser	Leu	Ile	Arg	Arg	Tyr	Pro	Lys	Glu	Ala	Ala	Val	Ala	Leu	
225					230					235					240	
Ala	Lys	Arg	Asn	Gly	Gly	Ile	Gln	Trp	Met	Asp	Val	Ser	Glu	Gly	Thr	
				245					250					255		
Val	Met	Asn	Glu	Ala	Val	Asn	Ala	Val	Ala	Ala	Ser	Ala	Leu	Ala	Pro	
			260					265					270			
Ser	Ala	Ser	Ala	Pro	Pro	Leu	Glu	Glu	Lys	Ser	Lys	Leu	Thr	Glu	Gln	
		275				280						285				
Ala	Met	Asp	Leu	Val	Thr	Ala	Ala	Glu	Pro	Glu	Ile	Ile	Ala	Ser	Leu	
	290					295					300					
Ala	Pro	Val	Pro	Ala	Pro	Val	Phe	Ala	Ile	Pro	Pro	Lys	Pro	Ala	Asp	
305					310					315					320	
Tyr	Asn	Val	Arg	Thr	Leu	Arg	Ile	Asp	Glu	Ala	Thr	Trp	Leu	Arg	Met	
			325						330					335		
Ile	Pro	Lys	Ser	Met	Asn	Thr	Pro	Phe	Gln	Ile	Gln	Val	Thr	Asp	Asn	
			340					345					350			
Thr	Gly	Thr	Asn	Trp	His	Leu	Asn	Leu	Arg	Gly	Gly	Thr	Arg	Val	Val	
		355					360					365				
Asn	Leu	Asp	Gln	Ile	Ala	Pro	Met	Arg	Phe	Val	Leu	Asp	Leu	Gly	Gly	
	370					375					380					
Lys	Ser	Tyr	Lys	Glu	Thr	Ser	Trp	Asp	Pro	Asn	Gly	Lys	Lys	Val	Gly	
385					390					395					400	
Phe	Ile	Val	Phe	Gln	Ser	Lys	Ile	Pro	Phe	Glu	Leu	Trp	Thr	Ala	Ala	
			405						410					415		
Ser	Gln	Ile	Gly	Gln	Ala	Thr	Val	Val	Asn	Tyr	Val	Gln	Leu	Tyr	Ala	
			420					425					430			
Glu	Asp	Ser	Ser	Phe	Thr	Ala	Gln	Ser	Ile	Ile	Ala	Thr	Thr	Ser	Leu	

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435				440				445							
Ala	Tyr	Asn	Tyr	Glu	Pro	Glu	Gln	Leu	Asn	Lys	Thr	Asp	Pro	Glu	Met
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Asn	Tyr	Tyr	Leu	Leu	Ala	Thr	Phe	Ile	Asp	Ser	Ala	Ala	Ile	Thr	Pro
465					470				475						480
Thr	Asn	Met	Thr	Gln	Pro	Asp	Val	Trp	Asp	Ala	Leu	Leu	Thr	Met	Ser
				485					490					495	
Pro	Leu	Ser	Ala	Gly	Glu	Val	Thr	Val	Lys	Gly	Ala	Val	Val	Ser	Glu
			500					505					510		
Val	Val	Pro	Ala	Asp	Leu	Ile	Gly	Ser	Tyr	Thr	Pro	Glu	Ser	Leu	Asn
		515					520					525			
Ala	Ser	Leu	Pro	Asn	Asp	Ala	Ala	Arg	Cys	Met	Ile	Asp	Arg	Ala	Ser
	530					535					540				
Lys	Ile	Ala	Glu	Ala	Ile	Lys	Ile	Asp	Asp	Asp	Ala	Gly	Pro	Asp	Glu
545					550				555						560
Tyr	Ser	Pro	Asn	Ser	Val	Pro	Ile	Gln	Gly	Gln	Leu	Ala	Ile	Ser	Gln
			565						570					575	
Leu	Glu	Thr	Gly	Tyr	Gly	Val	Arg	Ile	Phe	Asn	Pro	Lys	Gly	Ile	Leu
			580					585					590		
Ser	Lys	Ile	Ala	Ser	Arg	Ala	Met	Gln	Ala	Phe	Ile	Gly	Asp	Pro	Ser
		595					600					605			
Thr	Ile	Ile	Thr	Gln	Ala	Ala	Pro	Val	Leu	Ser	Asp	Lys	Asn	Asn	Trp
	610					615					620				
Ile	Ala	Leu	Ala	Gln	Gly	Val	Lys	Thr	Ser	Leu	Arg	Thr	Lys	Ser	Leu
625					630					635					640
Ser	Ala	Gly	Val	Lys	Thr	Ala	Val	Ser	Lys	Leu	Ser	Ser	Ser	Glu	Ser
				645					650					655	
Ile	Gln	Asn	Trp	Thr	Gln	Gly	Phe	Leu	Asp	Lys	Val	Ser	Ala	His	Phe
		660						665					670		
Pro	Ala	Pro	Lys	Pro	Asp	Cys	Pro	Thr	Ser	Gly	Asp	Ser	Gly	Glu	Ser
		675					680					685			
Ser	Asn	Arg	Arg	Val	Lys	Arg	Asp	Ser	Tyr	Ala	Gly	Val	Val	Lys	Arg
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		20						25					30		
Gln	Ser	Phe	Thr	Pro	Ser	Val	Asp	Met	Ser	Gln	Ser	Arg	Glu	Phe	Leu
		35					40					45			
Thr	Lys	Ala	Ile	Glu	Gln	Gly	Ser	Met	Ser	Ile	Pro	Tyr	Gln	His	Val
50						55					60				
Asn	Val	Pro	Lys	Val	Asp	Arg	Lys	Val	Val	Ser	Leu	Val	Val	Arg	Pro
65					70					75					80
Phe	Ser	Ser	Gly	Ala	Phe	Ser	Ile	Ser	Gly	Val	Ile	Ser	Pro	Ala	His
			85						90					95	
Ala	Tyr	Leu	Leu	Glu	Cys	Leu	Pro	Gln	Leu	Glu	Gln	Ala	Met	Ala	Phe

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100						105				110					
Val	Ala	Ser	Pro	Glu	Ser	Phe	Gln	Ala	Ser	Asp	Val	Ala	Lys	Arg	Phe
		115					120					125			
Ala	Ile	Lys	Pro	Gly	Met	Ser	Leu	Gln	Asp	Ala	Ile	Thr	Ala	Phe	Ile
	130					135					140				
Asn	Phe	Val	Ser	Ala	Met	Leu	Lys	Met	Thr	Val	Thr	Arg	Gln	Asn	Phe
145					150					155					160
Asp	Val	Ile	Val	Ala	Glu	Ile	Glu	Arg	Leu	Ala	Ser	Thr	Ser	Val	Ser
				165					170					175	
Val	Arg	Thr	Glu	Glu	Ala	Lys	Val	Ala	Asp	Glu	Glu	Leu	Met	Leu	Phe
			180					185					190		
Gly	Leu	Asp	His	Arg	Gly	Pro	Gln	Gln	Leu	Asp	Val	Ser	Asp	Ala	Lys
		195					200					205			
Gly	Ile	Met	Lys	Ala	Ala	Asp	Ile	Gln	Thr	Thr	His	Asp	Val	His	Leu
	210					215					220				
Ala	Pro	Gly	Val	Gly	Asn	Ile	Asp	Pro	Glu	Ile	Tyr	Asn	Glu	Gly	Arg
225					230					235					240
Phe	Met	Phe	Met	Gln	His	Lys	Pro	Leu	Ala	Ala	Asp	Gln	Ser	Tyr	Phe
				245					250					255	
Thr	Leu	Glu	Thr	Ala	Asp	Tyr	Phe	Lys	Ile	Tyr	Pro	Thr	Tyr	Asp	Glu
			260					265					270		
His	Asp	Gly	Arg	Met	Ala	Asp	Gln	Lys	Gln	Ser	Gly	Leu	Ile	Leu	Cys
		275					280					285			
Thr	Lys	Asp	Glu	Val	Leu	Ala	Glu	Gln	Thr	Ile	Phe	Lys	Leu	Asp	Ala
	290					295					300				
Pro	Asp	Asp	Lys	Thr	Val	His	Leu	Leu	Asp	Arg	Asp	Asp	Asp	His	Val
305					310					315					320
Val	Ala	Arg	Phe	Thr	Lys	Val	Phe	Ile	Glu	Asp	Val	Ala	Pro	Gly	His
				325					330					335	
His	Ala	Ala	Gln	Arg	Ser	Gly	Gln	Arg	Ser	Val	Leu	Asp	Asp	Leu	Tyr
			340					345					350		
Ala	Asn	Thr	Gln	Val	Ile	Ser	Ile	Thr	Ser	Ala	Ala	Leu	Lys	Trp	Val
		355					360					365			
Val	Lys	His	Gly	Val	Ser	Asp	Gly	Ile	Val	Asn	Arg	Lys	Asn	Val	Lys
	370					375					380				
Val	Cys	Val	Gly	Phe	Asp	Pro	Leu	Tyr	Thr	Leu	Ser	Thr	His	Asn	Gly
385					390					395					400
Val	Ser	Leu	Cys	Ala	Leu	Leu	Met	Asp	Glu	Lys	Leu	Ser	Val	Leu	Asn
				405					410					415	
Ser	Ala	Cys	Arg	Met	Thr	Leu	Arg	Ser	Leu	Met	Lys	Thr	Gly	Arg	Asp
			420					425					430		
Val	Asp	Ala	His	Arg	Ala	Phe	Gln	Arg	Val	Leu	Ser	Gln	Gly	Tyr	Thr
		435					440					445			
Ser	Leu	Met	Cys	Tyr	Tyr	His	Pro	Ser	Arg	Lys	Leu	Ala	Tyr	Gly	Glu
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Val	Leu	Phe	Leu	Glu	Arg	Ser	Asn	Asp	Val	Thr	Asp	Gly	Ile	Lys	Leu
465					470					475					480
Gln	Leu	Asp	Ala	Ser	Arg	Gln	Cys	His	Glu	Cys	Pro	Val	Leu	Gln	Gln
				485					490					495	
Lys	Val	Val	Glu	Leu	Glu	Lys	Gln	Ile	Ile	Met	Gln	Lys	Ser	Ile	Gln
		500						505					510		
Ser	Asp	Pro	Thr	Pro	Val	Ala	Leu	Gln	Pro	Leu	Leu	Ser	Gln	Leu	Arg
		515					520						525		

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Glu	Leu	Ser	Ser	Glu	Val	Thr	Arg	Leu	Gln	Met	Glu	Leu	Ser	Arg	Ala
530						535					540				
Gln	Ser	Leu	Asn	Ala	Gln	Leu	Glu	Ala	Asp	Val	Lys	Ser	Ala	Gln	Ser
545					550					555					560
Cys	Ser	Leu	Asp	Met	Tyr	Leu	Arg	His	His	Thr	Cys	Ile	Asn	Gly	His
				565					570					575	
Ala	Lys	Glu	Asp	Glu	Leu	Leu	Asp	Ala	Val	Arg	Val	Ala	Pro	Asp	Val
			580					585					590		
Arg	Arg	Glu	Ile	Met	Glu	Lys	Arg	Ser	Glu	Val	Arg	Gln	Gly	Trp	Cys
		595					600					605			
Glu	Arg	Ile	Ser	Lys	Glu	Ala	Ala	Ala	Lys	Cys	Gln	Thr	Val	Ile	Asp
610					615						620				
Asp	Leu	Thr	Leu	Met	Asn	Gly	Lys	Gln	Ala	Gln	Glu	Ile	Thr	Glu	Leu
625					630					635					640
Arg	Asp	Ser	Ala	Glu	Lys	Tyr	Glu	Lys	Gln	Ile	Ala	Glu	Leu	Val	Ser
				645					650					655	
Thr	Ile	Thr	Gln	Asn	Gln	Ile	Thr	Tyr	Gln	Gln	Glu	Leu	Gln	Ala	Leu
			660					665					670		
Val	Ala	Lys	Asn	Val	Glu	Leu	Asp	Ala	Leu	Asn	Gln	Arg	Gln	Ala	Lys
		675					680					685			
Ser	Leu	Arg	Ile	Thr	Pro	Ser	Leu	Leu	Ser	Ala	Thr	Pro	Ile	Asp	Ser
690						695					700				
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Ser	Gly	Ile	Thr	Asp	Gln	Ser	Asn	Asp	Val	Phe	Glu	Asp	Ala	Ala	Lys
			20				25						30		
Ala	Phe	Ser	Met	Phe	Thr	Arg	Ser	Asp	Val	Tyr	Lys	Ala	Leu	Asp	Glu
			35				40					45			
Ile	Pro	Phe	Ser	Asp	Asp	Ala	Met	Leu	Pro	Ile	Pro	Pro	Thr	Ile	Tyr
50						55					60				
Thr	Lys	Pro	Ser	His	Asp	Ser	Tyr	Tyr	Tyr	Ile	Asp	Ala	Leu	Asn	Arg
65					70					75					80
Val	Arg	Arg	Lys	Thr	Tyr	Gln	Gly	Pro	Asp	Asp	Val	Tyr	Val	Pro	Asn
				85					90					95	
Cys	Ser	Ile	Val	Glu	Leu	Leu	Glu	Pro	His	Glu	Thr	Leu	Thr	Ser	Tyr
			100					105					110		
Gly	Arg	Leu	Ser	Glu	Ala	Ile	Glu	Asn	Arg	Ala	Lys	Asp	Gly	Asp	Ser
			115				120					125			
Gln	Ala	Arg	Ile	Ala	Thr	Thr	Tyr	Gly	Arg	Ile	Ala	Glu	Ser	Gln	Ala
						135						140			
Arg	Gln	Ile	Lys	Ala	Pro	Leu	Glu	Lys	Phe	Val	Leu	Ala	Leu	Leu	Val
145					150					155					160
Ala	Glu	Ala	Gly	Gly	Ser	Leu	Tyr	Asp	Pro	Val	Leu	Gln	Lys	Tyr	Asp
				165					170					175	
Glu	Ile	Pro	Asp	Leu	Ser	His	Asn	Cys	Pro	Leu	Trp	Cys	Phe	Arg	Glu

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180				185				190							
Ile	Cys	Arg	His	Ile	Ser	Gly	Pro	Leu	Pro	Asp	Arg	Ala	Pro	Tyr	Leu
		195					200					205			
Tyr	Leu	Ser	Ala	Gly	Val	Phe	Trp	Leu	Met	Ser	Pro	Arg	Met	Thr	Ser
	210					215					220				
Ala	Ile	Pro	Pro	Leu	Leu	Ser	Asp	Leu	Val	Asn	Leu	Ala	Ile	Leu	Gln
225					230					235					240
Gln	Thr	Ala	Gly	Leu	Asp	Pro	Ser	Leu	Val	Lys	Leu	Gly	Val	Gln	Ile
				245					250					255	
Cys	Leu	His	Ala	Ala	Ala	Ser	Ser	Ser	Tyr	Ala	Trp	Phe	Ile	Leu	Lys
			260					265					270		
Thr	Lys	Ser	Ile	Phe	Pro	Gln	Asn	Thr	Leu	His	Ser	Met	Tyr	Glu	Ser
		275					280					285			
Leu	Glu	Gly	Gly	Tyr	Cys	Pro	Asn	Leu	Glu	Trp	Leu	Glu	Pro	Arg	Ser
	290					295					300				
Asp	Tyr	Lys	Phe	Met	Tyr	Met	Gly	Val	Met	Pro	Leu	Ser	Ala	Lys	Tyr
305					310					315					320
Ala	Arg	Ser	Ala	Pro	Ser	Asn	Asp	Lys	Lys	Ala	Arg	Glu	Leu	Gly	Glu
				325					330					335	
Lys	Tyr	Gly	Leu	Ser	Ser	Val	Val	Gly	Glu	Leu	Arg	Lys	Arg	Thr	Lys
			340					345					350		
Thr	Tyr	Val	Lys	His	Asp	Phe	Ala	Ser	Val	Arg	Tyr	Ile	Arg	Asp	Ala
		355					360					365			
Met	Ala	Cys	Thr	Ser	Gly	Ile	Phe	Leu	Val	Arg	Thr	Pro	Thr	Glu	Thr
	370					375					380				
Val	Leu	Gln	Glu	Tyr	Thr	Gln	Ser	Pro	Glu	Ile	Lys	Val	Pro	Ile	Pro
385					390					395					400
Gln	Lys	Asp	Trp	Thr	Gly	Pro	Ile	Gly	Glu	Ile	Arg	Ile	Leu	Lys	Asp
				405					410					415	
Thr	Thr	Ser	Ser	Ile	Ala	Arg	Tyr	Leu	Tyr	Arg	Thr	Trp	Tyr	Leu	Ala
			420					425					430		
Ala	Ala	Arg	Met	Ala	Ala	Gln	Pro	Arg	Thr	Trp	Asp	Pro	Leu	Phe	Gln
		435					440					445			
Ala	Ile	Met	Arg	Ser	Gln	Tyr	Val	Thr	Ala	Arg	Gly	Gly	Ser	Gly	Ala
	450					455					460				
Ala	Leu	Arg	Glu	Ser	Leu	Tyr	Ala	Ile	Asn	Val	Ser	Leu	Pro	Asp	Phe
465					470					475					480
Lys	Gly	Leu	Pro	Val	Lys	Ala	Ala	Thr	Lys	Ile	Phe	Gln	Ala	Ala	Gln
				485					490					495	
Leu	Ala	Asn	Leu	Pro	Phe	Ser	His	Thr	Ser	Val	Ala	Ile	Leu	Ala	Asp
			500					505					510		
Thr	Ser	Met	Gly	Leu	Arg	Asn	Gln	Val	Gln	Arg	Arg	Pro	Arg	Ser	Ile
		515					520					525			
Met	Pro	Leu	Asn	Val	Pro	Gln	Gln	Gln	Val	Ser	Ala	Pro	His	Thr	Leu
						535					540				
Thr	Ala	Asp	Tyr	Ile	Asn	Tyr	His	Met	Asn	Leu	Ser	Thr	Thr	Ser	Gly
545					550					555					560
Ser	Ala	Val	Ile	Glu	Lys	Val	Ile	Pro	Leu	Gly	Val	Tyr	Ala	Ser	Ser
				565					570					575	
Pro	Pro	Asn	Gln	Ser	Ile	Asn	Ile	Asp	Ile	Ser	Ala	Cys	Asp	Ala	Ser
			580					585					590		
Ile	Thr	Trp	Asp	Phe	Phe	Leu	Ser	Val	Ile	Met	Ala	Ala	Ile	His	Glu
							600					605			

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Gly	Val	Ala	Ser	Ser	Ser	Ile	Gly	Lys	Pro	Phe	Met	Gly	Val	Pro	Ala	
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625					630					635					640	
Ile	Ser	Gly	Met	Gln	Asn	Met	Ile	Gln	His	Leu	Ser	Lys	Leu	Tyr	Lys	
				645					650					655		
Arg	Gly	Phe	Ser	Tyr	Arg	Val	Asn	Asp	Ser	Phe	Ser	Pro	Gly	Asn	Asp	
			660					665					670			
Phe	Thr	His	Met	Thr	Thr	Thr	Phe	Pro	Ser	Gly	Ser	Thr	Ala	Thr	Ser	
		675					680					685				
Thr	Glu	His	Thr	Ala	Asn	Asn	Ser	Thr	Met	Met	Glu	Thr	Phe	Leu	Thr	
	690					695					700					
Val	Trp	Gly	Pro	Glu	His	Thr	Asp	Asp	Pro	Asp	Val	Leu	Arg	Leu	Met	
705					710					715					720	
Lys	Ser	Leu	Thr	Ile	Gln	Arg	Asn	Tyr	Val	Cys	Gln	Gly	Asp	Asp	Gly	
				725					730					735		
Leu	Met	Ile	Ile	Asp	Gly	Thr	Thr	Ala	Gly	Lys	Val	Asn	Ser	Glu	Thr	
			740					745					750			
Ile	Gln	Lys	Met	Leu	Glu	Leu	Ile	Ser	Lys	Tyr	Gly	Glu	Glu	Phe	Gly	
		755					760					765				
Trp	Lys	Tyr	Asp	Ile	Ala	Tyr	Asp	Gly	Thr	Ala	Glu	Tyr	Leu	Lys	Leu	
	770					775					780					
Tyr	Phe	Ile	Phe	Gly	Cys	Arg	Ile	Pro	Asn	Leu	Ser	Arg	His	Pro	Ile	
785					790					795					800	
Val	Gly	Lys	Glu	Arg	Ala	Asn	Ser	Ser	Ala	Glu	Glu	Pro	Trp	Pro	Ala	
				805					810					815		
Ile	Leu	Asp	Gln	Ile	Met	Gly	Val	Phe	Phe	Asn	Gly	Val	His	Asp	Gly	
			820					825					830			
Leu	Gln	Trp	Gln	Arg	Trp	Ile	Arg	Tyr	Ser	Trp	Ala	Leu	Cys	Cys	Ala	
		835					840					845				
Phe	Ser	Arg	Gln	Arg	Thr	Met	Ile	Gly	Glu	Ser	Val	Gly	Tyr	Leu	Gln	
	850					855					860					
Tyr	Pro	Met	Trp	Ser	Phe	Val	Tyr	Trp	Gly	Leu	Pro	Leu	Val	Lys	Ala	
865					870					875					880	
Phe	Gly	Ser	Asp	Pro	Trp	Ile	Phe	Ser	Trp	Tyr	Met	Pro	Thr	Gly	Asp	
				885					890					895		
Leu	Gly	Met	Tyr	Ser	Trp	Ile	Ser	Leu	Ile	Arg	Pro	Leu	Met	Thr	Arg	
			900					905					910			
Trp	Met	Val	Ala	Asn	Gly	Tyr	Val	Thr	Asp	Arg	Cys	Ser	Pro	Val	Phe	
		915					920					925				
Gly	Asn	Ala	Asp	Tyr	Arg	Arg	Cys	Phe	Asn	Glu	Leu	Lys	Leu	Tyr	Gln	
	930					935					940					
Gly	Tyr	Tyr	Met	Ala	Gln	Leu	Pro	Arg	Asn	Pro	Lys	Lys	Ser	Gly	Arg	
945					950					955					960	
Ala	Ala	Pro	Arg	Glu	Val	Arg	Glu	Gln	Phe	Thr	Gln	Ala	Leu	Ser	Asp	
				965					970					975		
Tyr	Leu	Leu	Gln	Asn	Pro	Glu	Leu	Lys	Ser	Arg	Val	Leu	Arg	Gly	Arg	
			980					985					990			
Ser	Glu	Trp	Glu	Lys	Tyr	Gly	Ala	Gly	Ile	Ile	His	Asn	Pro	Pro	Ser	
		995					1000					1005				
Leu	Phe	Asp	Val	Pro	His	Lys	Trp	Tyr	Gln	Gly	Ala	Gln	Glu	Ala	Ala	
	1010						1015				1020					
Ile	Ala	Thr	Arg	Glu	Glu	Leu	Ala	Glu	Met	Asp	Glu	Thr	Leu	Met	Arg	
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Ala	Arg	Arg	His	Arg	Tyr	Ser	Ser	Phe	Ser	Lys	Leu	Leu	Glu	Ala	Tyr	
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Leu	Leu	Val	Lys	Trp	Arg	Met	Cys	Glu	Ala	Arg	Glu	Pro	Ser	Val	Asp	
			1060					1065					1070			
Leu	Arg	Leu	Pro	Leu	Cys	Ala	Gly	Ile	Asp	Pro	Leu	Asn	Ser	Asp	Pro	
			1075				1080					1085				
Phe	Leu	Lys	Met	Val	Ser	Val	Gly	Pro	Met	Leu	Gln	Ser	Thr	Arg	Lys	
			1090				1095				1100					
Tyr	Phe	Ala	Gln	Thr	Leu	Phe	Met	Ala	Lys	Thr	Val	Ser	Gly	Leu	Asp	
1105					1110					1115					1120	
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Ala	Thr	Gly	Val	Ala	Val	Asp	Ile	Tyr	Leu	Glu	Asp	Ile	His	Gly	Gly	
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Asp	Trp	Glu	Arg	Phe	Met	Arg	Glu	Lys	Leu	Arg	Val	Leu	Lys	Tyr	Glu	
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Asn	Tyr	Ser	Asn	Asp	Asp	Asp	Asp	Pro	Pro	Leu	Phe	Ala	Lys	Asp	Leu
			180					185					190		
Ser	Asp	Tyr	Ala	Lys	Ala	Phe	Tyr	Ser	Asp	Thr	Tyr	Glu	Val	Leu	Asp
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Met	Val	Ser	Ala	Pro	Pro	Tyr	Ile	Ile	Asn	Ala	Thr	Asp	Ala	Met	Leu
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His	Tyr	Ile	Glu	Gln	Lys	Ile	Leu	Pro	Asn	Ile	Thr	Ser	Tyr	Met	Leu		
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		180						185					190			
Pro	Leu	Asp	Leu	Asp	Ala	His	Val	Ala	Ser	His	Gly	Leu	His	Gly	Asn	
		195					200					205				
Met	Thr	Leu	Thr	Ser	Ser	Asp	Ile	Gln	Arg	His	Ile	Thr	Glu	Phe	Ile	
	210					215					220					
Ser	Ser	Trp	Gln	Asn	His	Pro	Ile	Val	Gln	Val	Ser	Ala	Asp	Val	Glu	
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Gln	Leu	Leu	Asn	Thr	Glu	Thr	Leu	Ser	Val	Arg	Gly	Ala	Asn	Pro	Leu	
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930				935				940							
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Thr	Ala	Ala	Thr	Phe	Ala	Glu	Trp	Val	Asn	Thr	Ser	Met	Lys	Thr	Ala
				965					970					975	
Phe	Asp	Leu	Ser	Asp	Met	Leu	Leu	Glu	Pro	Leu	Leu	Ser	Gly	Asp	Pro
			980					985					990		
Arg	Met	Thr	Gln	Leu	Ala	Ile	Gln	Tyr	Gln	Gln	Tyr	Asn	Gly	Arg	Thr
		995					1000					1005			
Phe	Asn	Ile	Ile	Pro	Glu	Met	Pro	Gly	Ser	Val	Ile	Ala	Asp	Cys	Val
1010						1015					1020				
Gln	Leu	Thr	Ala	Glu	Val	Phe	Asn	His	Glu	Tyr	Asn	Leu	Phe	Gly	Ile
1025					1030					1035					1040
Ala	Arg	Gly	Asp	Ile	Ile	Ile	Gly	Arg	Val	Gln	Ser	Thr	His	Leu	Trp
				1045					1050					1055	
Ser	Pro	Leu	Ala	Pro	Pro	Pro	Asp	Leu	Val	Phe	Asp	Arg	Asp	Thr	Pro
			1060					1065					1070		
Gly	Val	His	Ile	Phe	Gly	Arg	Asp	Cys	Arg	Ile	Ser	Phe	Gly	Met	Asn
	1075					1080						1085			
Gly	Ala	Ala	Pro	Met	Ile	Arg	Asp	Glu	Thr	Gly	Leu	Met	Val	Pro	Phe
1090					1095						1100				
Glu	Gly	Asn	Trp	Ile	Phe	Pro	Leu	Ala	Leu	Trp	Gln	Met	Asn	Thr	Arg
1105				1110						1115					1120
Tyr	Phe	Asn	Gln	Gln	Phe	Asp	Ala	Trp	Ile	Lys	Thr	Gly	Glu	Leu	Arg
			1125						1130					1135	
Ile	Arg	Ile	Glu	Met	Gly	Ala	Tyr	Pro	Tyr	Met	Leu	His	Tyr	Tyr	Asp
		1140					1145						1150		
Pro	Arg	Gln	Tyr	Ala	Asn	Ala	Trp	Asn	Leu	Thr	Ser	Ala	Trp	Leu	Glu
	1155					1160						1165			
Glu	Ile	Thr	Pro	Thr	Ser	Ile	Pro	Ser	Val	Pro	Phe	Met	Val	Pro	Ile
1170					1175						1180				
Ser	Ser	Asp	His	Asp	Ile	Ser	Ser	Ala	Pro	Ala	Val	Gln	Tyr	Ile	Ile
1185				1190					1195					1200	
Ser	Thr	Glu	Tyr	Asn	Asp	Arg	Ser	Leu	Phe	Cys	Thr	Asn	Ser	Ser	Ser
			1205						1210				1215		
Pro	Gln	Thr	Ile	Ala	Gly	Pro	Asp	Lys	His	Ile	Pro	Val	Glu	Arg	Tyr
		1220						1225					1230		
Asn	Ile	Leu	Thr	Asn	Pro	Asp	Ala	Pro	Pro	Thr	Gln	Ile	Gln	Leu	Pro
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Glu	Val	Val	Asp	Leu	Tyr	Asn	Val	Val	Thr	Arg	Tyr	Ala	Tyr	Glu	Thr
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<210> SEQ ID NO 22
<211> LENGTH: 3854
<212> TYPE: DNA
<213> ORGANISM: Reovirus

<400> SEQUENCE: 22

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tctatgttta ctcgcagcga tgtctacaag gcgctggatg aaataccttt ctctgatgat	180
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tggcagcggg	ggatacggtta	ttcatgggct	ctatgctgtg	ctttctcacg	tcaaagaaca	2580
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gtggctaata gttacgtaac tgacagatgc tcaaccgtat tcgggaacgc agattatcgc	2820
aggtgtttca atgaacttaa actatatcaa ggttattata tggcacaatt gcccaggaat	2880
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<210> SEQ ID NO 23															
<211> LENGTH: 1267															
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<213> ORGANISM: Reovirus															
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Ala	Phe	Ser	Met	Phe	Thr	Arg	Ser	Asp	Val	Tyr	Lys	Ala	Leu	Asp	Glu
			35				40					45			
Ile	Pro	Phe	Ser	Asp	Asp	Ala	Met	Leu	Pro	Ile	Pro	Pro	Thr	Ile	Tyr
			50				55				60				
Thr	Lys	Pro	Ser	His	Asp	Ser	Tyr	Tyr	Tyr	Ile	Asp	Ala	Leu	Asn	Arg
65					70					75				80	
Val	Arg	Arg	Lys	Thr	Tyr	Gln	Gly	Pro	Asp	Asp	Val	Tyr	Val	Pro	Asn
				85					90					95	
Cys	Ser	Ile	Val	Glu	Leu	Leu	Glu	Pro	His	Glu	Thr	Leu	Thr	Ser	Tyr
			100					105					110		
Gly	Arg	Leu	Ser	Glu	Ala	Ile	Glu	Asn	Arg	Ala	Lys	Asp	Gly	Asp	Ser
			115				120					125			
Gln	Ala	Arg	Ile	Ala	Thr	Thr	Tyr	Gly	Arg	Ile	Ala	Glu	Ser	Gln	Ala
			130				135				140				
Arg	Gln	Ile	Lys	Ala	Pro	Leu	Glu	Lys	Phe	Val	Leu	Ala	Leu	Leu	Val
145					150					155				160	

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Ala	Glu	Ala	Gly	Gly	Ser	Leu	Tyr	Asp	Pro	Val	Leu	Gln	Lys	Tyr	Asp	
				165					170					175		
Glu	Ile	Pro	Asp	Leu	Ser	His	Asn	Cys	Pro	Leu	Trp	Cys	Phe	Arg	Glu	
			180					185					190			
Ile	Cys	Arg	His	Ile	Ser	Gly	Pro	Leu	Pro	Asp	Arg	Ala	Pro	Tyr	Leu	
		195					200					205				
Tyr	Leu	Ser	Ala	Gly	Val	Phe	Trp	Leu	Met	Ser	Pro	Arg	Met	Thr	Ser	
	210					215					220					
Ala	Ile	Pro	Pro	Leu	Leu	Ser	Asp	Leu	Val	Asn	Leu	Ala	Ile	Leu	Gln	
225					230				235						240	
Gln	Thr	Ala	Gly	Leu	Asp	Pro	Ser	Leu	Val	Lys	Leu	Gly	Val	Gln	Ile	
				245					250					255		
Cys	Leu	His	Ala	Ala	Ala	Ser	Ser	Ser	Tyr	Ser	Trp	Phe	Ile	Leu	Lys	
			260					265					270			
Thr	Lys	Ser	Ile	Phe	Pro	Gln	Asn	Thr	Leu	His	Ser	Met	Tyr	Glu	Ser	
	275						280					285				
Leu	Glu	Gly	Gly	Tyr	Cys	Pro	Asn	Leu	Glu	Trp	Leu	Glu	Pro	Arg	Ser	
	290					295					300					
Asp	Tyr	Lys	Phe	Met	Tyr	Met	Gly	Val	Met	Pro	Leu	Ser	Ala	Lys	Tyr	
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Ala	Arg	Ser	Ala	Pro	Ser	Asn	Asp	Lys	Lys	Ala	Arg	Glu	Leu	Gly	Glu	
				325					330					335		
Lys	Tyr	Gly	Leu	Ser	Ser	Val	Val	Gly	Glu	Leu	Arg	Lys	Arg	Thr	Lys	
			340					345					350			
Thr	Tyr	Val	Lys	His	Asp	Phe	Ala	Ser	Val	Arg	Tyr	Ile	Arg	Asp	Ala	
		355					360					365				
Met	Ala	Cys	Thr	Ser	Gly	Ile	Phe	Leu	Val	Arg	Thr	Pro	Thr	Glu	Thr	
	370					375					380					
Val	Leu	Gln	Glu	Tyr	Thr	Gln	Ser	Pro	Glu	Ile	Lys	Val	Pro	Ile	Pro	
385					390					395					400	
Gln	Lys	Asp	Trp	Thr	Gly	Pro	Ile	Gly	Glu	Ile	Arg	Ile	Leu	Lys	Asp	
				405					410					415		
Thr	Thr	Ser	Ser	Ile	Ala	Arg	Tyr	Leu	Tyr	Arg	Thr	Trp	Tyr	Leu	Ala	
			420					425					430			
Ala	Ala	Arg	Met	Ala	Ala	Gln	Pro	Arg	Thr	Trp	Asp	Pro	Leu	Phe	Gln	
		435					440					445				
Ala	Ile	Met	Arg	Ser	Gln	Tyr	Val	Thr	Ala	Arg	Gly	Gly	Ser	Gly	Ala	
	450					455					460					
Ala	Leu	Arg	Glu	Ser	Leu	Tyr	Ala	Ile	Asn	Val	Ser	Leu	Pro	Asp	Phe	
465					470					475					480	
Lys	Gly	Leu	Pro	Val	Lys	Ala	Ala	Thr	Lys	Ile	Phe	Gln	Ala	Ala	Gln	
			485						490					495		
Leu	Ala	Asn	Leu	Pro	Phe	Ser	His	Thr	Ser	Val	Ala	Ile	Leu	Ala	Asp	
		500						505					510			
Thr	Ser	Met	Gly	Leu	Arg	Asn	Gln	Val	Gln	Arg	Arg	Pro	Arg	Ser	Ile	
	515						520					525				
Met	Pro	Leu	Asn	Val	Pro	Gln	Gln	Gln	Val	Ser	Ala	Pro	His	Thr	Leu	
	530					535					540					
Thr	Ala	Asp	Tyr	Ile	Asn	Tyr	His	Met	Asn	Leu	Ser	Pro	Thr	Ser	Gly	
545					550					555					560	
Ser	Ala	Val	Ile	Glu	Lys	Val	Ile	Pro	Leu	Gly	Val	Tyr	Ala	Ser	Ser	
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580						585						590							
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Gly	Val	Ala	Ser	Ser	Ser	Ile	Gly	Lys	Pro	Phe	Met	Gly	Val	Pro	Ala				
610						615						620							
Ser	Ile	Val	Asn	Asp	Glu	Ser	Val	Val	Gly	Val	Arg	Ala	Ala	Arg	Pro				
625						630						635						640	
Ile	Ser	Gly	Met	Gln	Asn	Met	Ile	Gln	His	Leu	Ser	Lys	Leu	Tyr	Lys				
645						650						655							
Arg	Gly	Phe	Ser	Tyr	Arg	Val	Asn	Asp	Ser	Phe	Ser	Pro	Gly	Asn	Asp				
660						665						670							
Phe	Thr	His	Met	Thr	Thr	Thr	Phe	Pro	Ser	Gly	Ser	Thr	Ala	Thr	Ser				
675						680						685							
Thr	Glu	His	Thr	Ala	Asn	Asn	Ser	Thr	Met	Met	Glu	Thr	Phe	Leu	Thr				
690						695						700							
Val	Trp	Gly	Pro	Glu	His	Thr	Asp	Asp	Pro	Asp	Val	Leu	Arg	Leu	Met				
705						710						715						720	
Lys	Ser	Leu	Thr	Ile	Gln	Arg	Asn	Tyr	Val	Cys	Gln	Gly	Asp	Asp	Gly				
725						730						735							
Leu	Met	Ile	Ile	Asp	Gly	Thr	Thr	Ala	Gly	Lys	Val	Asn	Ser	Glu	Thr				
740						745						750							
Ile	Gln	Asn	Asp	Leu	Glu	Leu	Ile	Ser	Lys	Tyr	Gly	Glu	Glu	Phe	Gly				
755						760						765							
Trp	Lys	Tyr	Asp	Ile	Ala	Tyr	Asp	Gly	Thr	Ala	Glu	Tyr	Leu	Lys	Leu				
770						775						780							
Tyr	Phe	Ile	Phe	Gly	Cys	Arg	Ile	Pro	Asn	Leu	Ser	Arg	His	Pro	Ile				
785						790						795						800	
Val	Gly	Lys	Glu	Arg	Ala	Asn	Ser	Ser	Ala	Glu	Glu	Pro	Trp	Pro	Ala				
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Ile	Leu	Asp	Gln	Ile	Met	Gly	Val	Phe	Phe	Asn	Gly	Val	His	Asp	Gly				
820						825						830							
Leu	Gln	Trp	Gln	Arg	Trp	Ile	Arg	Tyr	Ser	Trp	Ala	Leu	Cys	Cys	Ala				
835						840						845							
Phe	Ser	Arg	Gln	Arg	Thr	Met	Ile	Gly	Glu	Ser	Val	Gly	Tyr	Leu	Gln				
850						855						860							
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865						870						875						880	
Phe	Gly	Ser	Asp	Pro	Trp	Ile	Phe	Ser	Trp	Tyr	Met	Pro	Thr	Gly	Asp				
885						890						895							
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915						920						925							
Gly	Asn	Ala	Asp	Tyr	Arg	Arg	Cys	Phe	Asn	Glu	Leu	Lys	Leu	Tyr	Gln				
930						935						940							
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945						950						955						960	
Ala	Ala	Ser	Arg	Glu	Val	Arg	Glu	Gln	Phe	Thr	Gln	Ala	Leu	Ser	Asp				
965						970						975							
Tyr	Leu	Met	Gln	Asn	Pro	Glu	Leu	Lys	Ser	Arg	Val	Leu	Arg	Gly	Arg				
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1090 1095 1100	
Tyr Phe Ala Gln Thr Leu Phe Met Ala Lys Thr Val Ser Gly Leu Asp	
1105 1110 1115 1120	
Val Asn Ala Ile Asp Ser Ala Leu Leu Arg Leu Arg Thr Leu Gly Ala	
1125 1130 1135	
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1140 1145 1150	
Ser Glu Ala Asp Ala Leu Ala Gly Lys Ile Met Leu Gln Asp Val Asn	
1155 1160 1165	
Thr Val Gln Leu Ala Arg Val Val Asn Leu Ala Val Pro Asp Thr Trp	
1170 1175 1180	
Met Ser Leu Asp Phe Asp Ser Met Phe Lys His His Val Lys Leu Leu	
1185 1190 1195 1200	
Pro Lys Asp Gly Arg His Leu Asn Thr Asp Ile Pro Pro Arg Met Gly	
1205 1210 1215	
Trp Leu Arg Ala Ile Leu Arg Phe Leu Gly Ala Gly Met Val Met Thr	
1220 1225 1230	
Ala Thr Gly Val Ala Val Asp Ile Tyr Leu Glu Asp Ile His Gly Gly	
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agggatggga caaaacaatc tcagcacagc cagatatgat ggtatgtggt ggcgcgTcg	180
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gtgttactgc tactggaag cggggTatgc tgccttCgt tgcgcagatg cacgagatga	360
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<212> TYPE: PRT	
<213> ORGANISM: Reovirus	
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20 25 30	
Asp Lys Thr Ile Ser Ala Gln Pro Asp Met Met Val Cys Gly Gly Ala	
35 40 45	
Val Val Cys Met His Cys Leu Gly Val Val Gly Ser Leu Gln Arg Lys	
50 55 60	
Leu Lys His Leu Pro His His Arg Cys Asn Gln Gln Ile Arg His Gln	
65 70 75 80	
Asp Tyr Val Asp Val Gln Phe Ala Asp Arg Val Thr Ala His Trp Lys	
85 90 95	
Arg Gly Met Leu Ser Phe Val Ala Gln Met His Glu Met Met Asn Asp	
100 105 110	
Val Ser Pro Asp Asp Leu Asp Arg Val Arg Thr Glu Gly Gly Ser Leu	
115 120 125	
Val Glu Leu Asn Arg Leu Gln Val Asp Pro Asn Ser Met Phe Arg Ser	
130 135 140	
Ile His Ser Ser Trp Thr Asp Pro Leu Gln Val Val Asp Asp Leu Asp	
145 150 155 160	
Thr Lys Leu Asp Gln Tyr Trp Thr Ala Leu Asn Leu Met Ile Asp Ser	
165 170 175	
Ser Asp Leu Ile Pro Asn Phe Met Met Arg Asp Pro Ser His Ala Phe	
180 185 190	
Asn Gly Val Lys Leu Glu Gly Asp Ala Arg Gln Thr Gln Phe Ser Arg	
195 200 205	
Thr Phe Asp Ser Arg Ser Ser Leu Glu Trp Gly Val Met Val Tyr Asp	
210 215 220	
Tyr Ser Glu Leu Glu His Asp Pro Ser Lys Gly Arg Ala Tyr Arg Lys	
225 230 235 240	
Glu Leu Val Thr Pro Ala Arg Asp Phe Gly His Phe Gly Leu Ser His	
245 250 255	
Tyr Ser Arg Ala Thr Thr Pro Ile Leu Gly Lys Met Pro Ala Val Phe	
260 265 270	
Ser Gly Met Leu Thr Gly Asn Cys Lys Met Tyr Pro Phe Ile Lys Gly	
275 280 285	

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tgagctcatc	tgagtctatc	cagaattgga	ctcaaggatt	cttggataaa	gtgtcagcgc	2040
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<400> SEQUENCE: 27

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Gly	Asn	Val	Phe 20	Lys	Pro	Ser	Ala	Glu 25	Thr	Ser	Ser	Thr	Ala 30	Val	Pro
Ser	Leu 35	Ser	Leu	Ser	Pro	Gly	Met 40	Leu	Asn	Pro	Gly	Gly 45	Val	Pro	Trp
Ile 50	Ala	Val	Gly	Asp	Glu	Thr 55	Ser	Val	Thr	Ser	Pro 60	Gly	Ala	Leu	Arg
Arg 65	Met	Thr	Ser	Lys	Asp 70	Ile	Pro	Glu	Thr	Ala 75	Ile	Ile	Asn	Thr	Asp 80
Asn	Ser	Ser	Gly 85	Ala	Val	Pro	Ser	Glu	Ser 90	Ala	Leu	Val	Pro	Tyr 95	Ile
Asp	Glu	Pro	Leu 100	Val	Val	Val	Thr	Glu 105	His	Ala	Ile	Thr	Asn 110	Phe	Thr
Lys	Ala 115	Glu	Met	Ala	Leu	Glu	Phe 120	Asn	Arg	Glu	Phe	Leu 125	Asp	Lys	Met
Arg 130	Val	Leu	Ser	Val	Ser 135	Pro	Lys	Tyr	Ser	Asp	Leu 140	Leu	Thr	Tyr	Val
Asp 145	Cys	Tyr	Val	Gly 150	Val	Ser	Ala	Arg	Gln	Ala 155	Leu	Asn	Asn	Phe	Gln 160
Lys	Gln	Val	Pro	Val 165	Ile	Thr	Pro	Thr	Arg 170	Gln	Thr	Met	Tyr	Val 175	Asp
Ser	Ile	Gln 180	Ala	Ala	Leu	Lys	Ala 185	Leu	Glu	Lys	Trp	Glu	Ile 190	Asp	Leu
Arg	Val 195	Ala	Gln	Thr	Leu	Leu	Pro 200	Thr	Asn	Val	Pro	Ile 205	Gly	Glu	Val
Ser 210	Cys	Pro	Met	Gln	Ser 215	Val	Val	Lys	Leu	Leu	Asp 220	Asp	Gln	Leu	Pro
Asp 225	Asp	Thr	Leu	Ile 230	Arg	Arg	Tyr	Pro	Lys	Glu 235	Ala	Ala	Val	Ala	Leu 240
Ala	Lys	Arg	Asn 245	Gly	Gly	Ile	Gln	Trp	Met 250	Asp	Val	Ser	Glu	Gly 255	Thr
Val	Met	Asn 260	Glu	Ala	Val	Asn	Ala 265	Val	Ala	Ala	Ser	Ala	Leu	Ala	Pro
Ser	Ala 275	Ser	Ala	Pro	Pro	Leu	Glu 280	Glu	Lys	Ser	Lys	Leu 285	Thr	Glu	Gln

Ala	Met	Asp	Leu	Val	Thr	Ala	Ala	Glu	Pro	Glu	Ile	Ile	Ala	Ser	Leu	
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Ala	Pro	Val	Pro	Ala	Pro	Val	Phe	Ala	Ile	Pro	Pro	Lys	Pro	Ala	Asp	
305		310					315					320				
Tyr	Asn	Val	Arg	Thr	Leu	Arg	Ile	Asp	Glu	Ala	Thr	Trp	Leu	Arg	Met	
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Ile	Pro	Lys	Ser	Met	Asn	Thr	Pro	Phe	Gln	Ile	Gln	Val	Thr	Asp	Asn	
			340		345					350						
Thr	Gly	Thr	Asn	Trp	His	Leu	Asn	Leu	Arg	Gly	Gly	Thr	Arg	Val	Val	
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Lys	Ser	Tyr	Lys	Glu	Thr	Ser	Trp	Asp	Pro	Asn	Gly	Lys	Lys	Val	Gly	
385		390					395					400				
Phe	Ile	Val	Phe	Gln	Ser	Lys	Ile	Pro	Phe	Glu	Leu	Trp	Thr	Ala	Ala	
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Ser	Gln	Ile	Gly	Gln	Ala	Thr	Val	Val	Asn	Tyr	Val	Gln	Leu	Tyr	Ala	
			420		425					430						
Glu	Asp	Ser	Ser	Phe	Thr	Ala	Gln	Ser	Ile	Ile	Ala	Thr	Thr	Ser	Leu	
		435		440					445							
Ala	Tyr	Asn	Tyr	Glu	Pro	Glu	Gln	Leu	Asn	Lys	Thr	Asp	Pro	Glu	Met	
450		455					460									
Asn	Tyr	Tyr	Leu	Leu	Ala	Thr	Phe	Ile	Asp	Ser	Ala	Ala	Ile	Thr	Pro	
465		470					475					480				
Thr	Asn	Met	Thr	Gln	Pro	Asp	Val	Trp	Asp	Ala	Leu	Leu	Thr	Met	Ser	
			485		490					495						
Pro	Leu	Ser	Ala	Gly	Glu	Val	Thr	Val	Lys	Gly	Ala	Val	Val	Ser	Glu	
			500		505					510						
Val	Val	Pro	Ala	Asp	Leu	Ile	Gly	Ser	Tyr	Thr	Pro	Glu	Ser	Leu	Asn	
		515		520					525							
Ala	Ser	Leu	Pro	Asn	Asp	Ala	Ala	Arg	Cys	Met	Ile	Asp	Arg	Ala	Ser	
530		535					540									
Lys	Ile	Ala	Glu	Ala	Ile	Lys	Ile	Asp	Asp	Asp	Ala	Gly	Pro	Asp	Glu	
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Tyr	Ser	Pro	Asn	Ser	Val	Pro	Ile	Gln	Gly	Gln	Leu	Ala	Ile	Ser	Gln	
			565		570					575						
Leu	Glu	Thr	Gly	Tyr	Gly	Val	Arg	Ile	Phe	Asn	Pro	Lys	Gly	Ile	Leu	
			580		585					590						
Ser	Lys	Ile	Ala	Ser	Arg	Ala	Met	Gln	Ala	Phe	Ile	Gly	Asp	Pro	Ser	
595		600					605									
Thr	Ile	Ile	Thr	Gln	Ala	Ala	Pro	Val	Leu	Ser	Asp	Lys	Asn	Asn	Trp	
610		615					620									
Ile	Ala	Leu	Ala	Gln	Gly	Val	Lys	Thr	Ser	Leu	Arg	Thr	Lys	Ser	Leu	
625		630					635					640				
Ser	Ala	Gly	Val	Lys	Thr	Ala	Val	Ser	Lys	Leu	Ser	Ser	Ser	Glu	Ser	
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Ile	Gln	Asn	Trp	Thr	Gln	Gly	Phe	Leu	Asp	Lys	Val	Ser	Ala	His	Phe	
			660		665					670						
Pro	Ala	Pro	Lys	Pro	Asp	Cys	Pro	Thr	Ser	Gly	Asp	Ser	Gly	Glu	Ser	
675		680					685									
Ser	Asn	Arg	Arg	Val	Lys	Arg	Asp	Ser	Tyr	Ala	Gly	Val	Val	Lys	Arg	
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<210> SEQ ID NO 28
<211> LENGTH: 2304
<212> TYPE: DNA
<213> ORGANISM: Reovirus

<400> SEQUENCE: 28

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<210> SEQ ID NO 29						
<211> LENGTH: 736						
<212> TYPE: PRT						
<213> ORGANISM: Reovirus						
<400> SEQUENCE: 29						
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						30
Asn	Asp	Val	Ser	Tyr	Gln	Asp
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						45
Tyr	Met	Leu	Asp	Gly	Tyr	Glu
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						60
His	Lys	Asn	Trp	Leu	His	His
65					70	
						75
						80
Ser	Gln	Leu	Leu	Glu	Tyr	Trp
				85		
						90
						95
Asn	Val	Asp	Arg	Arg	Leu	Arg
			100			105
						110
Arg	Lys	Asp	Asp	Glu	Tyr	Asn
						120
						125
Asp	Val	Tyr	Ala	Pro	Leu	Ile
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						140
Ile	Gln	Asn	Leu	Asn	Arg	Gly
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Val	Ile	Gly	Ala	Arg	Ile	Leu
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Ser	Thr	Leu	Ser	Phe	Thr	Met
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						185
						190
Glu	Val	Gly	Arg	Val	Pro	His
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Ser	Ile	Ala	Thr	Pro	Lys	Cys
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Ser	Ile	Pro	Asn	Glu	Phe	Ile
225						230
						235
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Val	His	Ala	Asn	Ile	Leu	Asn
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						250
						255
Met	Ile	Asn	Arg	Lys	Arg	Leu
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						265
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Ala	Ala	Gln	Leu	Met	His	Leu
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						280
						285
His	Val	Asp	Val	Tyr	Lys	Val
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						300
Val	Asp	Val	Ala	Asp	Gly	Leu
305						310
						315
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His	Thr	Val	Pro	Val	Cys	Ile
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						330
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Asp	Tyr	Cys	Ile	Arg	Gln	Glu
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						345
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	370					375					380				
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Asp	Ile	Tyr	Asp	Phe	Val	Lys	Pro	Ile	Gly	Ala	Val	Leu	Pro	Lys	Gly
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Ser	Phe	Lys	Ser	Thr	Ile	Met	Arg	Val	Leu	Asp	Ser	Ile	Ser	Ile	Leu
			420					425					430		
Gly	Ile	Gln	Ile	Met	Pro	Arg	Ala	His	Val	Val	Asp	Ser	Asp	Glu	Val
		435					440					445			
Gly	Glu	Gln	Met	Glu	Pro	Thr	Phe	Glu	Gln	Ala	Val	Met	Glu	Ile	Tyr
	450					455					460				
Lys	Gly	Ile	Ala	Gly	Val	Asp	Ser	Leu	Asp	Asp	Leu	Ile	Lys	Trp	Val
465					470					475					480
Leu	Asn	Ser	Asp	Leu	Ile	Pro	His	Asp	Asp	Arg	Leu	Gly	Gln	Leu	Phe
				485					490					495	
Gln	Ala	Phe	Leu	Pro	Leu	Ala	Lys	Asp	Leu	Leu	Ala	Pro	Met	Ala	Arg
			500					505					510		
Lys	Phe	Tyr	Asp	Asn	Ser	Met	Ser	Glu	Gly	Arg	Leu	Leu	Thr	Phe	Ala
		515					520						525		
His	Ala	Asp	Ser	Glu	Leu	Leu	Asn	Ala	Asn	Tyr	Phe	Gly	His	Leu	Leu
	530						535				540				
Arg	Leu	Lys	Ile	Pro	Tyr	Ile	Thr	Glu	Val	Asn	Leu	Met	Ile	Arg	Lys
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Asn	Arg	Glu	Gly	Gly	Glu	Leu	Phe	Gln	Leu	Val	Leu	Ser	Tyr	Leu	Tyr
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Lys	Met	Tyr	Ala	Thr	Ser	Ala	Gln	Pro	Lys	Trp	Phe	Gly	Ser	Leu	Leu
			580					585					590		
Arg	Leu	Leu	Ile	Cys	Pro	Trp	Leu	His	Met	Glu	Lys	Leu	Ile	Gly	Glu
	595						600					605			
Ala	Asp	Pro	Ala	Ser	Thr	Ser	Ala	Glu	Ile	Gly	Trp	His	Ile	Pro	Arg
	610						615				620				
Glu	Gln	Leu	Met	Gln	Asp	Gly	Trp	Cys	Gly	Cys	Glu	Asp	Gly	Phe	Ile
625					630					635					640
Pro	Tyr	Val	Ser	Ile	Arg	Ala	Pro	Arg	Leu	Val	Ile	Glu	Glu	Leu	Met
				645					650					655	
Glu	Lys	Asn	Trp	Gly	Gln	Tyr	His	Ala	Gln	Val	Ile	Val	Thr	Asp	Gln
				660				665					670		
Leu	Val	Val	Gly	Glu	Pro	Arg	Arg	Val	Ser	Ala	Lys	Ala	Val	Ile	Lys
		675					680					685			
Gly	Asn	His	Leu	Pro	Val	Lys	Leu	Val	Ser	Arg	Phe	Ala	Cys	Phe	Thr
	690					695					700				
Leu	Thr	Ala	Lys	Tyr	Glu	Met	Arg	Leu	Ser	Cys	Gly	His	Ser	Thr	Gly
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<210> SEQ ID NO 30
<211> LENGTH: 418
<212> TYPE: PRT
<213> ORGANISM: Reovirus

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Gln Asn Val Pro Ile Asn Asp Glu Leu Ser Ser His Leu Leu Arg Ala
20 25 30

Gly Asn Ser Pro Trp Gln Leu Thr Gln Phe Leu Asp Trp Ile Ser Leu
35 40 45

Gly Arg Gly Leu Ala Thr Ser Ala Leu Val Pro Thr Ala Gly Ser Arg
50 55 60

Tyr Tyr Gln Met Ser Cys Leu Leu Ser Gly Thr Leu Gln Ile Pro Phe
65 70 75 80

Arg Pro Asn His Arg Trp Gly Asp Ile Arg Phe Leu Arg Leu Val Trp
85 90 95

Ser Ala Pro Thr Leu Asp Gly Leu Val Val Ala Pro Pro Gln Val Leu
100 105 110

Ala Gln Pro Ala Leu Gln Ala Gln Ala Asp Arg Val Tyr Asp Cys Asp
115 120 125

Asp Tyr Pro Phe Leu Ala Arg Asp Pro Arg Phe Lys His Arg Val Tyr
130 135 140

Gln Gln Leu Ser Ala Val Thr Leu Leu Asn Leu Thr Gly Phe Gly Pro
145 150 155 160

Ile Ser Tyr Val Arg Val Asp Glu Asp Met Trp Ser Gly Asp Val Asn
165 170 175

Gln Leu Leu Met Asn Tyr Phe Gly His Thr Phe Ala Glu Ile Ala Tyr
180 185 190

Thr Leu Cys Gln Ala Ser Ala Asn Arg Pro Trp Glu Tyr Asp Gly Thr
195 200 205

Tyr Ala Arg Met Thr Gln Ile Val Leu Ser Leu Phe Trp Leu Ser Tyr
210 215 220

Val Gly Val Ile His Gln Gln Asn Thr Tyr Arg Thr Phe Tyr Phe Gln
225 230 235 240

Cys Asn Arg Arg Gly Asp Ala Ala Glu Val Trp Ile Leu Ser Cys Ser
245 250 255

Leu Asn His Ser Ala Gln Ile Arg Pro Gly Asn Arg Ser Leu Phe Val
260 265 270

Met Pro Thr Ser Pro Asp Trp Asn Met Asp Val Asn Leu Ile Leu Ser
275 280 285

Ser Thr Leu Thr Gly Cys Leu Cys Ser Gly Ser Gln Leu Pro Leu Ile
290 295 300

Asp Asn Asn Ser Val Pro Ala Val Ser Arg Asn Ile His Gly Trp Thr
305 310 315 320

Gly Arg Ala Gly Asn Gln Leu His Gly Phe Gln Val Arg Arg Met Val
325 330 335

Thr Glu Phe Cys Asp Arg Leu Arg Arg Asp Gly Val Met Thr Gln Ala
340 345 350

Gln Gln Asn Gln Val Glu Ala Leu Ala Asp Gln Thr Gln Gln Phe Lys
355 360 365

Arg Asp Lys Leu Glu Thr Trp Ala Arg Glu Asp Asp Gln Tyr Asn Gln
370 375 380

-continued

Ala	His	Pro	Asn	Ser	Thr	Met	Phe	Arg	Thr	Lys	Pro	Phe	Thr	Asn	Ala
385					390					395					400
Gln	Trp	Gly	Arg	Gly	Asn	Thr	Gly	Ala	Thr	Ser	Ala	Ala	Ile	Ala	Ala
				405					410					415	
Leu	Ile														

What is claimed is:

1. An isolated reovirus comprising one or more of the following polypeptides:

a) a sigma-3 polypeptide comprising SEQ ID NO:15;

b) a mu-1 polypeptide having at least one amino acid modification, wherein the at least one amino acid modification comprises an Asp at residue 73 numbered relative to SEQ ID NO:27 (GenBank Accession No. M20161.1); or

c) a mu-2 polypeptide having at least one amino acid modification, wherein the at least one amino acid modification comprises a Ser at residue 528 numbered relative to SEQ ID NO:29 (GenBank Accession No. AF461684.1).

2. The reovirus of claim 1, wherein the mu-1 polypeptide comprises SEQ ID NO:17.

3. The reovirus of claim 1, wherein the mu-2 polypeptide comprises SEQ ID NO:16.

4. An isolated reovirus comprising one or both of the following genome segments:

a) a S4 genome segment comprising SEQ ID NO:4; or

b) a M2 genome segment having at least one nucleic acid modification, wherein the at least one nucleic acid modification comprises a C at position 248, numbered relative to SEQ ID NO:26 (GenBank Accession No. M20161.1).

5. The reovirus of claim 4, wherein the M2 genome segment comprises SEQ ID NO:6.

6. An isolated reovirus comprising a M1 genome segment, wherein the M1 genome segment comprises SEQ ID NO:5.

7. The reovirus of claim 4, wherein the reovirus further comprises a M1 genome segment having at least one nucleic acid modification, wherein the at least one nucleic acid modification comprises a T at position 1595, numbered relative to SEQ ID NO:28 (GenBank Accession No. AF461684.1).

8. An isolated polypeptide selected from the group consisting of:

a) a polypeptide comprising an amino acid sequence of a reovirus sigma-3 polypeptide, wherein the sequence of the reovirus sigma-3 polypeptide comprises SEQ ID NO:15;

b) a polypeptide comprising an amino acid sequence of a reovirus mu-1 polypeptide, wherein the sequence of the reovirus mu-1 polypeptide comprises at least one amino acid modification, wherein the at least one amino acid modification comprises an Asp at residue 73 numbered relative to SEQ ID NO:27 (GenBank Accession No. M20161.1); and

c) a polypeptide comprising an amino acid sequence of a reovirus mu-2 polypeptide, wherein the sequence of the reovirus mu-2 polypeptide comprises at least one amino acid modification, wherein the at least one amino acid

modification comprises a Ser at residue 528 numbered relative to SEQ ID NO:29 (GenBank Accession No. AF461684.1).

9. The polypeptide of claim 8, wherein the mu-1 polypeptide comprises SEQ ID NO:17.

10. The polypeptide of claim 8, wherein the mu-2 polypeptide comprises SEQ ID NO:16.

11. An isolated nucleic acid molecule selected from the group consisting of:

a) a nucleic acid molecule comprising a nucleic acid sequence of a reovirus S4 genome segment, wherein the nucleic acid sequence of the reovirus S4 genome segment comprises SEQ ID NO:4; and

b) a nucleic acid molecule comprising a nucleic acid sequence of a reovirus M2 genome segment, wherein the nucleic acid sequence of the reovirus M2 genome segment comprises at least one nucleic acid modification, wherein the at least one nucleic acid modification comprises a C at position 248, numbered relative to SEQ ID NO: 26 (GenBank Accession No. M20161.1).

12. The nucleic acid molecule of claim 11, wherein the M1 genome segment comprises SEQ ID NO:5.

13. An isolated nucleic acid molecule comprising a nucleic acid sequence of a reovirus M2 genome segment, wherein the M2 genome segment comprises SEQ ID NO:6.

14. The isolated nucleic acid of claim 11, wherein the isolated nucleic acid molecule further comprises a nucleic acid sequence of a reovirus M1 genome segment, wherein the nucleic acid sequence of the reovirus M1 genome segment comprises at least one nucleic acid modification, wherein the at least one nucleic acid modification comprises a T at position 1595, numbered relative to SEQ ID NO:28 (GenBank Accession No. AF461684.1).

15. A method of treating a proliferative disorder in a patient, comprising: administering the reovirus of claim 1.

16. The method of claim 15, wherein the reovirus is administered in an amount effective to cause oncolysis.

17. The method of claim 15, further comprising at least one of the procedures selected from the group consisting of surgery, chemotherapy, radiation therapy, and immunosuppressive therapy.

18. The method of claim 15, wherein the reovirus or pharmaceutical composition is administered more than once.

19. The method of claim 15, wherein the reovirus or pharmaceutical composition is administered intravenously, intravascularly, intrathecally, intramuscularly, subcutaneously, intraperitoneally, topically, orally, rectally, vaginally, nasally, by direct injection, or by inhalation.

20. A method of treating a proliferative disorder in a patient, comprising administering the reovirus of claim 4.

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